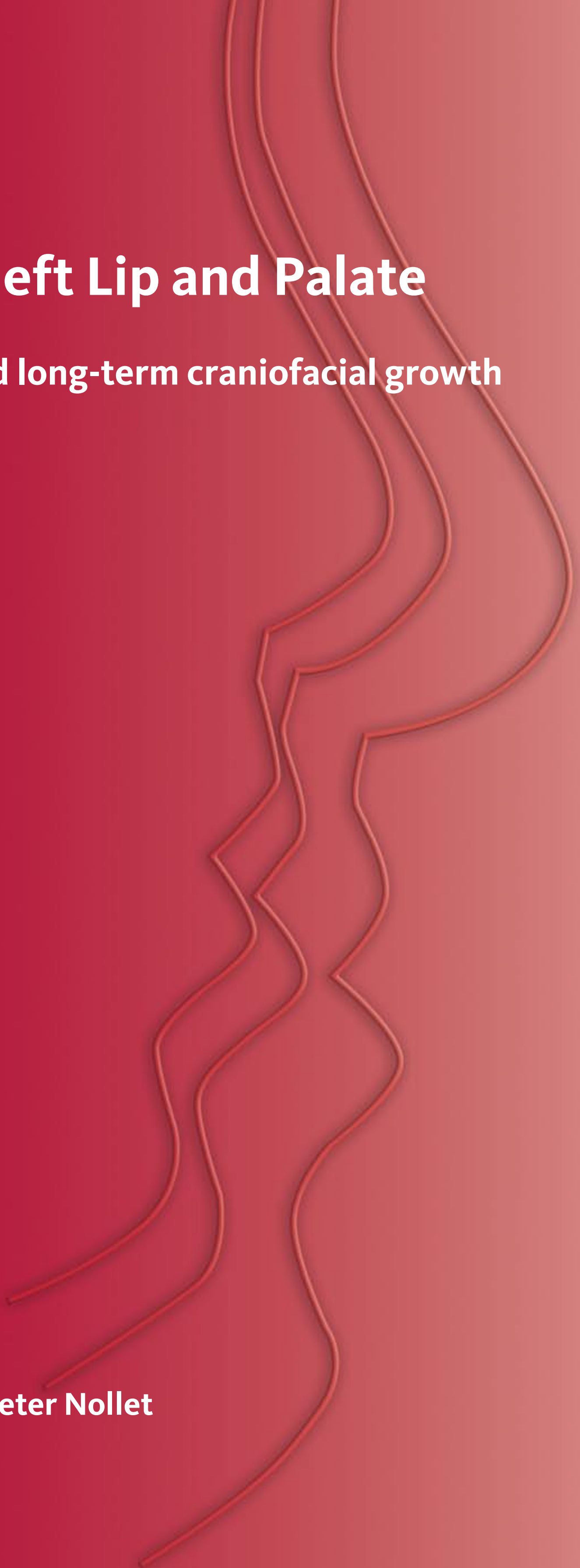
Unilateral Cleft Lip and Palate

Treatment outcome and long-term craniofacial growth



Pieter Nollet

Unilateral Cleft Lip And Palate

Treatment outcome and long-term craniofacial growth

Pieter Nollet

Pieter Nollet

Unilateral Cleft Lip And Palate
Treatment outcome and long-term craniofacial growth

Thesis Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
ISBN: 90-9020889-5

Cover illustration: modified from this thesis (Chapter 5)
Printed by: BENDA Drukkers, Wijchen, the Netherlands

Unilateral Cleft Lip And Palate

Treatment outcome and long-term craniofacial growth

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen,
op gezag van de Rector Magnificus prof. dr. C.W.P.M. Blom
volgens besluit van het College van Decanen
in het openbaar te verdedigen op maandag 6 november 2006
des namiddags om 15.30 uur precies

door

Petrus Josephus Paulinus Maria Nollet
geboren op 11 februari 1975
te Utrecht

Promotores:
Prof. dr. A.M. Kuijpers-Jagtman
Prof. dr. C. Katsaros

Manuscriptcommissie:
Prof. dr. P.H.M. Spauwen, voorzitter
Prof. dr. L.R. Dermaut (Rijksuniversiteit Gent, België)
Prof. dr. J.A. Sandham (UMC Groningen)

Promotiecommissie:
Dr. R. Admiraal
Prof. dr. S.J. Bergé
Prof. dr. H. Friede (University of Göteborg, Sweden)
Prof. dr. G. Semb (University of Manchester, UK)
Prof. dr. W.C. Shaw (University of Manchester, UK)

Paranimfen:
Drs. S. Henneman
Drs. R.W.F. Huyskens

The study presented in this thesis was conducted at the Department of Orthodontics and Oral Biology (Head: Prof. A.M. Kuijpers-Jagtman), College of Dental Science, and the Cleft Palate Craniofacial Unit (Head. Prof. A.M. Kuijpers-Jagtman) of the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. This study was part of the EUROCRAN project within the fifth Framework programme (FP5) of the European Union.

The College of Dental Science participates in the Netherlands Institute for Dental Sciences, acknowledged by the Royal Dutch Academy of Science KNAW.

Aan mijn ouders

Table of contents

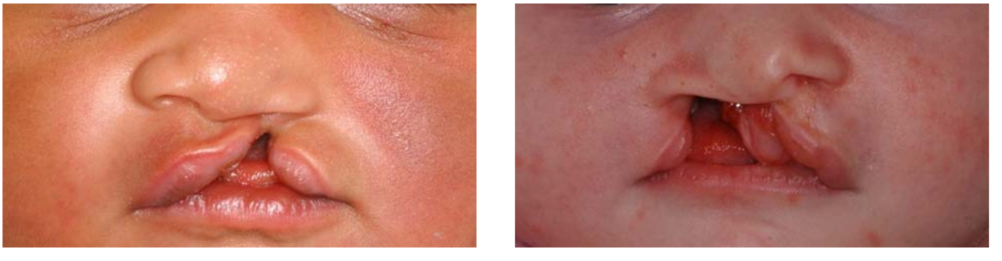
Chapter 1

General introduction

1.1 General Introduction

1.1.1 Types of clefts, incidence and etiology

Cleft lip and palate is the most widely known congenital facial deformity. Although cleft lip and palate occurs in various types, three main categories can be distinguished: isolated cleft lip and/or alveolus, isolated cleft palate, and combined cleft lip, alveolus and palate. Each category can be subdivided into complete and incomplete, unilateral or bilateral clefts. In some patients, lip clefting is not complete, but a soft tissue bridge is located either at the base of the nostril or between the segmented alveolar ridges (Figure 1.1). These soft tissue bands are called Simonart's bands and can occur in unilateral as well as bilateral clefts.[1] All types of clefts can vary greatly in development, size, shape and position. Figure 1.2 shows a palatal view of a baby born with a complete unilateral cleft lip and palate (UCLP).



A. *B.*

Figure 1.1. *Frontal views of a complete UCLP with (A) and without (B) a Simonart's band.*

The incidence of cleft lip and palate varies considerably among nationalities and races and depends also on the type of the cleft.[2,3] In the Netherlands, the incidence ranges from 1.4‰ to 1.8‰, which means that approximately 400 children are born with any type of cleft lip and palate in the Netherlands each year.[4-6] Males are more likely than females to have unilateral cleft lip and palate, while females have a slightly greater risk for cleft palate only.[7] The Simonart's band is more frequently observed in patients with an unilateral cleft compared to patients with bilateral clefts, and more in cleft lip than in cleft lip and palate.[1] The prevalence of the Simonart's band in patients with UCLP mentioned in literature ranges from 15.4% to 31.1%.[8-12]

Figure 1.2 *Palatal view of a baby born with a complete UCLP.*

Concerning the etiology of cleft lip and palate, there is general agreement upon the multifactorial heredity, which is partly due to genetic and partly due to environmental factors. The genetic component is suggested by the facts that relatives of individuals with clefts are at increased risk for having affected offspring[7] and that the risk for cleft lip and palate varies among races; orientals show a higher, and black people a lower incidence when compared with Caucasian people.[13] As far as the environmental component is concerned, many associations such as the socio-economic status, lifestyle factors as nutrition and smoking, health factors and illness have been recognized in the etiology of cleft lip and palate.[13-15] However, many environmental associations in literature are only reported once and several could not be reproduced in other studies, except for maternal age and maternal anticonvulsant therapy that would have an influence on the risk of having a child with a cleft lip and palate.[13,14] Further research is needed to elucidate the multifactorial etiology of orofacial clefts.

1.2. Maxillofacial characteristics of UCLP

1.2.1 Introduction

The three main groups of factors, which are known to influence facial morphology in cleft lip and palate, are intrinsic developmental deficiencies, functional distortions affecting the position and growth of both normal and abnormal parts, and iatrogenic factors introduced by treatment.[16] Intrinsic deficiencies are related to the presence of the cleft itself and are rarely of clinical significance. Functional growth factors, mainly from muscle activity before repair, seem mainly to cause facial asymmetries in UCLP and are usually reversible by surgical repair of the lip and palate. Comparisons between treated and non-treated cleft groups proved that iatrogenic factors are implicated as the major source of midfacial deficiency.[16]

1.2.2 Maxillofacial characteristics of unoperated UCLP

Because of the large range of variation within each type of cleft, it should be realized that the following description on the maxillofacial characteristics of unoperated UCLP is a general, *overall* description. Besides that, studies on groups with non-treated cleft groups are compromised by small sample sizes and sometimes by the inclusion of partly operated as well as totally unoperated cases.[17]

Persons with an unoperated complete UCLP demonstrate the combined effects of the presence of a cleft of the lip and alveolus (that is the premaxilla on the noncleft side being rotated ventrally) and the presence of a cleft palate where the maxilla and mandible are relatively retrusive accompanied by a steep mandibular plane.[18,19] In the maxillary arch, the relationship of the cleft segment to the noncleft segment varies from being normal to expressing various degrees of medial collapse, particularly in the canine area, causing an increased incidence of crossbite. On the noncleft side, the premaxillary segment has a tendency to rotate ventrally. There is also an increased incidence of scissors bite in the premolar area.[18] Simonart's bands do not interfere with the arrangement of the bundles of the orbicular oris muscle, ruptured at the cleft site, and seem to have a mild but positive influence on the final facial pattern in skeletal maturity in UCLP.[1]

When we compare unoperated complete unilateral cleft lip and palate with unoperated unilateral cleft lip and alveolus, a smaller arch width and a lesser arch depth have been observed in the complete cleft group. Moreover, in unoperated complete unilateral cleft lip and palate there is a tendency for the smaller segment to be positioned more cranially than in unoperated unilateral cleft lip and alveolus.[20-21]

Comparative studies between unoperated clefts and non-clefts indicate that patients with unoperated UCLP have relatively small retropositioned mandibles.[22] When compared with non-cleft groups, maxillary arch widths of unoperated complete UCLP groups were reduced, more anteriorly than posteriorly, resulting in more V-shaped arches.[23] This progressive reduction in maxillary arch widths in the anterior region of the cleft is consistent with the findings of Bishara et al.[18] and Latief.[17] Bishara et al.[18] reported a restricted maxillary canine region and a higher frequency of crossbites for patients with unoperated UCLP. Latief[17] found that the effect of a UCLP is mainly limited to the vicinity of the cleft in the anterior region.

1.2.3 Maxillofacial characteristics of operated UCLP

Treatment of patients with UCLP comprises several different orthopedic, surgical and orthodontic interventions that have an impact on the maxillofacial growth pattern. Since it is impossible to explain in this context all different interventions that influence maxillofacial growth, we limited ourselves to the intervention that is the most controversial, most discussed in literature and seems to have the most substantial impact on the maxillofacial growth pattern: the palate repair. In general, the most that can be concluded about the effect of palatal surgery on maxillofacial growth is that all palate repair procedures have the potential for some inhibitory effect in all three dimensions. This can be explained by the fact that most contemporary palate repair techniques attempt to minimize, but cannot completely eliminate palatal scarring, which is a primary factor in maxillofacial growth dysplasias. Many studies have attempted to relate growth results to specific techniques of cleft repair but, unfortunately, failed to do so, mainly because of major methodological drawbacks.[24]

With regard to maxillary growth, the issue of timing of palatal repair is also of important interest. Optimal timing of palatal closure could have an impact on the maxillofacial growth, which may result in dental arch relationships that can be treated conventionally, avoiding surgical correction of the skeletal bases.[25] With regard to the fact that the unoperated cleft maxilla exhibits near-normal growth potential and all palate repairs have the potential to disturb maxillary growth, it is logical to assume that delaying the procedure until the maxilla has completed most of its growth is a desirable approach. This approach, originally proposed by Schweckendiek[26] and modified by various authors since, involves early primary repair of the soft palate but postpones repair of the hard palate for 5 to 10 years (2-stage palatal closure with delayed closure of the hard palate). A number of investigations into subsequent maxillary growth have shown improved results compared with those following complete 1-stage early palate repair in infancy.[16,27,28] An issue of debate is the timing of hard palate closure in case of a 2-stage palatal closure procedure. Noverraz et al.[29] and Rohrich et al.[30] found no differences in growth results in comparative studies on 2-stage palatal closure between early and delayed hard palate closure groups, whereas Friede and Enemark[31] did find significant differences between those groups. Other issues in this controversy are the additional burdens of treatment and worse speech performance for cleft patients with delayed palatal closure of the hard palate.[30]

1.3 Multidisciplinary treatment of patients with UCLP

A cleft lip and palate is a structural defect that usually affects several functional areas. Complex problems may arise regarding the child's feeding, facial appearance, speech, hearing, dental functioning and social psychological development. These problems can be managed best by bringing together specialists from diverse disciplines to review the physical and psychological changes caused by the defect and to coordinate all treatment to the best advantage of the patient and his/her parents. Following the standards of the American Cleft Palate-Craniofacial Association (ACPA), the cleft team should minimally have an operating surgeon, an orthodontist and a speech-language pathologist. The staff of the interdisciplinary team may also include professionals from the following areas: anesthesiology, audiology, diagnostic medical imaging/radiology, genetic counselling, genetics/dysmorphology, neurology, neurosurgery, nursing, opthalmology, oral and maxillofacial surgery, otolaryngology, pediatrics, pediatric dentistry, physical anthropology, plastic surgery, prosthodontics, psychiatry, psychology and social work.[32] Optimal care for cleft patients is provided by teams that see sufficient numbers of patients each year to maintain clinical expertise in diagnosis and treatment.[32,33]

The first goal of the cleft team is to provide the optimal delivery of comprehensive care that offers the best overall chance of success for the cleft patients. A longitudinal treatment plan should be developed for each patient, which can be modified if necessitated by treatment progress or new therapeutic insights. Each interdisciplinary team should maintain centralized and comprehensive records on each patient. Tasks of the cleft team also comprise the provision of information to the parents, patients, primary care providers addressing feeding, peripheral worker, colleagues, researchers, and students. Therefore, an office with a secretary, listed telephone number and e-mail address should be maintained and a co-ordinator who facilitates the functions and efficiency of the team should be designated. Finally, a cleft team should provide and promote educational programs to train new team members in order to ensure continuity of cleft care.[32]

1.4. Evaluation of treatment outcome in UCLP

1.4.1 Single center versus intercenter research

Reports of single center studies have been by far the commonest form of presenting outcomes in cleft lip and palate. Intercenter research has, however, several advantages over single center research. Firstly, an intercenter study usually comprises more patients than a single center study, which allows more powerful statistics and enhances more reliable conclusions. Secondly, single center research is more susceptible to biases, especially analysis bias and reporting bias. Finally, an intercenter approach would stimulate the co-operative spirit and facilitate fruitful joint working, such as the development of rating scales and the formulation of new research questions. So, intercenter studies are more informative than single center reports, and will have an important future role in cleft care.[34] However, with regard to intercenter research, the logistic challenges and costs of meetings may be substantial. An alternative to intercenter collaborations for routine clinical audit could be the use of a digital “good practice archive” that is accessible through the Internet. Such an archive comprises relevant clinical records, which are considered representatives of good practice and enable comparisons between the center in question and the archive. However, the use of digital “good practice archives” requires the availability of evaluation methods that can be used over the Internet. A second alternative to intercenter comparisons is the use of a registry. This implies that a cleft center establishes a list of consecutive cases of newborn babies that could be compared with other cleft centers.[34]

1.4.2 Intercenter research in UCLP

An increase in the number of multicenter studies in UCLP can be observed over the past decades. These studies overcome, at least in part, some of the limitations and potential biases associated with the comparison of outcomes described in single center reports.[34] Some of the recent multicenter studies have in common that several components of treatment outcome (i.e. dental arch relationships, cephalometrics, nasolabial aspects) are evaluated separately and, subsequently, general conclusions about treatment outcome are given.[33,35,36] Additionally, other important issues in cleft care are examined like, for example, the organization of services, amount of treatment and treatment satisfaction. Key recommendations to local, national and international authorities can be made on the results of the multicenter comparative studies and, from this point of view, results of multicenter studies play an increasing role in the determination of policies in cleft care.[33]

Research designs vary considerably among recent and current intercenter UCLP studies. The initial Eurocleft study,[34] the Eurocleft follow-up study[34] and the CSAG study[33] are retrospective observational multicenter studies in the field of UCLP. Although valuable conclusions could be drawn from the results of these multicenter studies, it appeared not possible to ascribe success or failure to particular details of the surgical protocols. This problem had been overcome in the intercenter Dutchcleft study[37] and the multicenter Scandcleft project[38] where the effects of specific interventions are investigated by means of prospective randomized clinical trials. This illustrates that it depends on the research question which study design should be taken for multicenter comparison in cleft care. The effect of a specific intervention during cleft treatment could very well be answered in a randomized clinical trial whereas questions like “which treatment protocol yielded the best treatment outcome?” or “how is our center performing in relation to other cleft centers?” could preferably be answered in an observational set-up.

1.4.3 Systematic reviews and meta-analyses in UCLP

A systematic review is a formalized and stringent process of combining the information from all relevant studies (both published and unpublished) of the same health condition; these studies are usually clinical trials of similar treatments but may be observational studies. A meta-analysis is a particular type of systematic review that focuses on the numerical results. The main aim of a meta-analysis is to combine the results from individual studies to produce, if appropriate, an estimate of the overall effect or average effect of interest. A meta-analysis offers all the advantages of the systematic review. In particular, a meta-analysis, because of its inflated sample size, is able to detect treatment effects with greater power and estimate these effects with greater precision than any single study.[39,40]

It was attempted to collect all meta-analyses and systematic reviews in the field of operated unilateral cleft lip and palate with the outcome measures growth, dental arch relationships and nasolabial esthetics from the Cochrane databases (DARE and CENTRAL) and Medline (December 2005). In order to retrieve all available systematic reviews and meta-analyses that met the inclusion criteria, an optimal search strategy as developed by Montori et al.[41] was performed for the Medline search. Although a number of meta-analyses and systematic reviews in cleft lip and palate were found, mainly about the etiology of orofacial clefts, only one relevant publication met the inclusion criteria.[42] This publication was a systematic review into the effects of feeding interventions in babies with cleft lip and/or palate on growth, development and parental satisfaction. The study was retrieved from the Cochrane Database and included a total of 232 babies from four randomized controlled trials (RCTs) of feeding interventions for babies born with cleft lip, cleft palate or cleft lip and palate up to the age of 6 months.

Non-compatibility between cleft groups could be an explanation for the low number of meta-analyses in UCLP. This non-compatibility is mainly caused by small sample sizes, clinical heterogeneity among cleft groups and the definition and diversity of variables that influence treatment outcome. Other problems to perform a meta-analysis in cleft research are the lack of randomized clinical trials, inconsistent outcomes and result reporting, missing data, confounders, covariates, publication bias and varying quality in the designs and conducts of the examined studies. Although giving weight to the better cleft studies is one solution to the last problem, any weighting system can be criticized on the grounds that it is arbitrary.[40] Because of the problems mentioned above, a lot of research questions in cleft lip and palate have not been subjected to meta-analyses yet.

1.5 Objectives of the thesis

Treatment of children with a complete UCLP is complex and comprehensive. The range of treatment outcome is considerable and might be related to variation in sequence, timing, and technique of treatment, the organization and delivery of cleft care, as well as the skills and experience of individual surgeons. Therefore, it was the overall aim of this study to evaluate treatment outcome in UCLP.

The specific aims were:

- to evaluate and compare treatment outcome in an international setting with regard to dental arch relationships, facial esthetics and craniofacial development
- to compare patient records in an international setting and to select patients with good treatment outcome for the international "good practice archive"
- to test an alternative medium for rating dental arch relationships in UCLP, which would facilitate future intercenter evaluation of treatment outcome in cleft lip and palate
- to longitudinally evaluate treatment outcome in UCLP and determine if treatment outcome at a younger age could be predictive for treatment outcome/need for surgery at a later age

1.6 Overview of the thesis

The present retrospective longitudinal study was performed on the basis of consecutive patient data collected at the Cleft Palate Craniofacial Unit of the Radboud University Nijmegen Medical Centre, the Netherlands. All evaluated subjects were patients with a complete unilateral cleft lip and palate (UCLP) without Simonart's band and born between 1976 and 1986. All patients were life-long treated at the Nijmegen Cleft Palate Craniofacial Unit where they had to be registered within 3 months after birth and before any surgical intervention.

Chapter 1 introduces the topic of cleft lip and palate, and general aspects on the UCLP malformation are described. The background of this thesis is elucidated by a description of recent evaluations of treatment outcome in UCLP.

In *Chapter 2,* dental arch relationships of Nijmegen patients with a complete UCLP and treated with a two-stage palatal closure including delayed hard palate closure were evaluated and subsequently compared with the six centers from the Eurocleft study that used various treatment protocols. Relationships between timing of palatal closure and dental arch relationships were investigated for the Nijmegen patient group.

In *Chapter 3,* determinants for treatment outcome in UCLP were assessed by means of a meta-analysis of 1236 patients. The GOSLON Yardstick and the GOSLON-like “5-year-index” were used as rating systems to evaluate treatment results.

In *Chapter 4,* the reliability was investigated of using photographs of dental casts as an alternative to casts for rating dental arch relationships in UCLP.

In *Chapter 5,* the nasolabial appearance of the Nijmegen patients with UCLP has been evaluated at the age of 9 years and subsequently compared with the nasolabial outcome of the six-center Eurocleft study. Moreover, coherence between esthetic scorings and dental arch relationships was assessed.

In *Chapter 6,* the Nijmegen patient group was cephalometrically evaluated at the ages 9, 12 and 18 years, and it was attempted to explain cephalometric outcome at age 18 years with the help of cephalometric values at the ages 9 and 12 years. Moreover, the objective need for surgery at adulthood was related to the craniofacial morphology at the age of 9 years.

The general discussion, *Chapter 7*, relates and discusses the most noteworthy findings of the previous chapters. Some suggestions for future research are given.

1.7 References

1. Silva Filho OG, Santamaria M, Silva Dalhen G, Semb G. Prevalence of a Simonart’s band in patients with complete cleft lip and alveolus (CL) and complete cleft lip and palate (CLP). *Cleft Palate Craniofac J.* published online, 2005.
2. Fraser FC. Etiology of cleft lip and palate. In: Grabb WC, Rosenstein SW, Broch KR. Cleft lip and palate: surgical, dental and speech aspects. Boston: Little, Brown and Company; 1971:54-65.

3. Vanderas AP. Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review. *Cleft Palate J.* 1987;24:216-225.
4. Felix-Schollaart, Prahl-Andersen B, Puyenbroek JI, Boomsma DI. De incidentie van cheilo-gnatho-palatoschisis in Nederland. *Tijdschr Kindergeneeskunde.* 1986;54:90-95.
5. Van den Akker AMEA, Hoeksma JB, Prahl-Andersen B. Schisis in Nederland; de vraag naar behandeling van patienten met schisis. *Ned Tijdschr Tandheelkd.* 1987;94:520-525.
6. Anthony S, Dorrepaal CA, Kateman H, Van der Pal-de Bruin KM. Aangeboren afwijkingen in Nederland 1996-2003: gebaseerd op de landelijke verloskunde en neonatologie registraties. Leiden: TNO-PG;2005. Publ. nr. KvL/JPB 2005.152.
7. Natsume N, Kawai T, Ogi N, Yoshida W. Maternal risk factors in cleft lip and palate: case control study. *Br J Oral Maxillofac Surg.* 2000;38:23-25.
8. Nordin KE, Larson O, Nylen B, Eklund G. Early bone grafting in complete cleft lip and palate cases following maxillofacial orthopedics. 1. The method and the skeletal development from seven to thirteen years of age. *Scand J Plast Reconstr Surg.* 1983;17:33-50.
9. Smahel Z, Brejcha M. Differences in craniofacial morphology between complete and incomplete unilateral cleft lip and palate in adults. *Cleft Palate J.* 1983;20:113-127.
10. Semb G, Shaw WC. Simonart's band and facial growth in unilateral clefts of the lip and palate. *Cleft Palate Craniofac J.* 1991;28:40-48.
11. Silva Filho OG, Ramos AL, Abdo RCC. The influence of unilateral cleft lip and palate on maxillary dental arch morphology. *The Angle Orthodontist.* 1992;62:283-290.
12. Roberts-Harry D, Semb G, Hathorn I, Killingback N. Facial growth in patients with unilateral clefts of the lip and palate: a two-center study. *Cleft Palate Craniofac J.* 1996;33:489-493.
13. Derijcke A, Eerens A, Carels C. The incidence of oral clefts: a review. *Br J Oral Maxillofac Surg.* 1996;34:488-494.
14. Krapels IPC. The etiology of orofacial clefts. An emphasis on lifestyle and nutrition other than folate. PhD thesis. Radboud Universiteit Nijmegen. Enschede: PrintPartners Ipskamp; 2005.
15. Zeiger JS, Beaty TH, Liang KY. Oral clefts, maternal smoking, and TGFA: A meta-analysis of gene-environment interaction. *Cleft Palate Craniofac J.* 2005;42:58-63.

16. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Part 1: treatment affecting growth. *Cleft Palate J.* 1987;24:5-23.
17. Latief BS. Dental arch width in unoperated cleft patients. PhD thesis. University of Leiden. Wijchen: Benda Drukkers; 2005.
18. Bishara SE, de Arrendondo RS, Vaes HP, Jakobsen JR. Dentofacial relationships in persons with unoperated clefts: comparisons between three cleft types. *Am J Orthod.* 1985;87:481-507.
19. Hermann NV, Kreiborg S, Darvann TA, Jensen BL, Dahl E, Bolund S. Craniofacial morphology and growth comparisons in children with Robin Sequence, isolated cleft palate, and unilateral complete cleft lip and palate. *Cleft Palate Craniofac J.* 2003;40:373-396.
20. Bishara SE, Krause JC, Olin WH, Weston D, Van Ness J, Felling C. Facial and dental relationships of individuals with unoperated clefts of the lip and/or palate. *Cleft Palate J.* 1976;13:238-252.
21. Derijcke A, Kuijpers-Jagtman AM, Lekkas C. Hardjowasito W, Latief B. Dental arch dimensions in unoperated adult cleft-palate patients: an analysis of 37 cases. *J Craniofac Genet Dev Biol.* 1994;14:69-74.
22. Mars M, Houston WJB. A preliminary study of facial growth and morphology in unoperated male unilateral cleft lip and palate subjects over 13 years of age. *Cleft Palate J.* 1990;27:7-10.
23. McCance AM, Roberts-Harry D, Sherriff M, Mars M, Houston W. A study model analysis of adult unoperated Sri Lankas with unilateral cleft lip and palate. *Cleft Palate J.* 1990;27:146-154.
24. Kuijpers-Jagtman AM, Long RE. The influence of surgery and orthopedic treatment on maxillofacial growth and maxillary arch development in patients treated for orofacial clefts. *Cleft Palate Craniofac J.* 2000;37:527/1-12.
25. Hathorn I, Roberts-Harry D, Mars M. The Goslon yardstick applied to a consecutive series of patients with unilateral clefts of the lip and palate. *Cleft Palate Craniofac J.* 1996;33:494-496.
26. Schweckendiek H. Zur Frage der Früh- und Spätoperation der angeborenen Lippen–kiefer-Gaumen-spalten. *Z Laryng.* 1951;30:51-56.
27. Friede H, Moller M, Lilja J, Lauritzen C, Johanson B. Facial morphology and occlusion at the stage of early mixed dentition in cleft lip and palate patients treated with delayed closure of the hard palate. *Scand J Plast Reconstr Surg Hand Surg.* 1987;21:65-71.

28. Wada T, Tachimura T, Satoh K, Hara H, Hatano M, Sayan NB, Tatsuta U. Maxillary growth after two-stage palatal closure in complete (unilateral and bilateral) clefts of the lip and palate from infancy until 10 years of age. *J Osaka Univ Dent Sch.* 1990;30:53-63.
29. Noverraz AE, Kuijpers-Jagtman AM, Mars M, Van't Hof MA. Timing of hard palate closure and dental arch relationsips in unilateral cleft lip and palate patients: a mixed-longitudinal study. *Cleft Palate Craniofac J.* 1993;30:391-396.
30. Rohrich RJ, Rowsell AR, Johns DF, Drury MA, Grieg G, Watson DJ, Dodfrey AM, Poole MD. Timing of hard palatal closure: a critical long-term analysis. *Plast Reconstr Surg*. 1996;98:236-246.
31. Friede H, Enemark H. Long-term evidence for favorable midfacial growth after delayed hard palate repair in UCLP patients. *Cleft Palate J.* 2001;38:323-329.
32. American Cleft Palate-Craniofacial Association. Parameters for evaluation and treatment of patients with cleft lip/palate or other craniofacial anomalies. Chapel Hill (NC): American Cleft Palate-Craniofacial Association; 2000.
33. Sandy J, Williams A, Mildinhall S, Murphy T, Bearn D, Shaw B, Sell D, Devlin B, Murray J. The Clincal Standards Advisory Group (CSAG) Cleft Lip and Palate Study. *Br J Orthod.* 1998;25:21-30.
34. Shaw WC, Dahl E, Asher-McDade C, Brattström V, Mars M, McWilliam J, Mølsted K, Plint DA, Prahl-Andersen B, Roberts C, Semb G, The RPS. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 5. General discussion and conclusions. *Cleft Palate Craniofac J*. 1992;29:413-418.
35. Shaw WC, Brattström V, Mølsted K, Prahl-Andersen B, Roberts CT, Semb G. The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 5: Discussion and conclusions. *Cleft Palate Craniofac J*. 2005;42:93-98.
36. Shaw WC, Semb G. Eurocleft - An experiment in intercenter collaboration. In: Berkowitz S: *Cleft lip and palate*. Berlin Heidelberg: Springer; 2006:765-776.
37. Kuijpers-Jagtman AM, Prahl-Andersen B: History of neonatal maxillary orthopedics: Past to present. In: Berkowitz, S: Cleft lip and palate. Berlin Heidelberg: Springer; 2006: 395-407.
38. Semb, G. Multicenter trials in cleft lip and palate surgery. Presented at the International Collaboration on Craniofacial Anomalies, World Health Organization, Geneva, Switzerland, March 5-8, 2000.

39. Altman DG. Practical statistics for medical research. London: Chapman & Hall/CRC; 1991.
40. Petrie A, Sabin C. Medical Statistics at a glance. London: Blackwell Science Ltd; 2000.
41. Montori VM, Wilczynski NL, Morgan D, Haynes RB. Optimal search strategies for retrieving systematic reviews from Medline: analytical survey. *BMJ.* 2005;330(7482):68.
42. Glenny AM, Hooper L, Shaw WC, Reilly S, Kasem S, Reid J. Feeding interventions for growth and development in infants with cleft lip, cleft palate or cleft lip and palate. *Cochrane Database Syst Rev.* 2004;3:CD003315.

Chapter 2

Treatment outcome after two-stage palatal closure in unilateral cleft lip and palate: A comparison with Eurocleft

Pieter JPM Nollet
Christos Katsaros
Martin A van 't Hof
Gunvor Semb
William C Shaw
Anne Marie Kuijpers-Jagtman

Cleft Palate Craniofac J. 2005;42:512-516

Summary

Objective: To evaluate dental arch relationships of patients with unilateral cleft lip and palate (UCLP) treated with a two-stage palatal closure and to compare them with the six centers from the Eurocleft study that used various treatment protocols.
Design: Repeated-measures study.
Setting: Cleft Palate Craniofacial Unit of Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
Patients: Records of 9-year-old children with complete unilateral cleft lip and palate (n=43) were included.
Interventions: The dental arch relationships of these patients were assessed by applying the GOSLON Yardstick and subsequently compared with the GOSLON outcome of the six-center Eurocleft study.
Mean outcome measures: Statistics of intra- and interexaminer agreement.
Results: For the Nijmegen UCLP group, 9% of dental arch relationships had a GOSLON score of 1, 52% had a score of 2, 30% has a score of 3, 9% had a score of 4, and none had a score of 5. The mean Nijmegen GOSLON score showed no significant differences with Eurocleft centers A, B, and E, which achieved the best treatment results, but did significantly differ from GOSLON outcomes of Eurocleft centers D ($p<.001$), C, and F ($p<.01$), which had relatively poor treatment outcome.
Conclusions: Treatment outcome of the patients in the Nijmegen UCLP group treated with two-stage palatal closure was comparable with the results of the Eurocleft centers with the best outcome. Treatment protocol could not explain differences in the quality of treatment results.

2.1 Introduction

Although the need for highly specialized treatment of patients with cleft lip and palate (CLP) is widely recognized, there is still no generally accepted treatment protocol.[1] A six-center European comparative study of treatment outcome of children with unilateral CLP (UCLP) revealed that, in addition to different treatment protocols, obvious disparity was in the quality of results among the participating centers.[2]

One of the aspects of treatment on which no consensus exists is the timing of palatal closure. Some investigators advocate early hard palate closure,[3,4] whereas others suggest that delayed hard palate closure would result in more favorable growth of the maxilla.[5-8] Ross[9] concludes from his multicenter study that variation in the timing and technique of hard palate repair within the first decade of life does not affect growth appreciably, but he also emphasizes the importance of palatal closure for psychological reasons and speech development.

However, in spite of all previous research, the method and timing of palatal closure remains controversial. This could be seen in the 1996 to 2000 Eurocleft project, where 23 soft palate closure techniques and 21 hard palate closure techniques in the 201 registered centers were used. The timing of independently performed soft palate closures varied from birth to 3 years of age, the timing of independently performed hard palate closures varied from birth to 13 years of age, and the timing of hard and soft palate closure when performed simultaneously varied from 3 months to 3 years of age.[10] This illustrates the need for more investigations on the effect of the timing of palatal closure on the treatment outcome.

The aim of this study was to evaluate dental arch relationships of patients with UCLP treated with a two-stage palatal closure, including delayed closure of the hard palate, and to compare them with the six centers from the Eurocleft study that used various treatment protocols.

2.2 Subjects and methods

2.2.1 Subjects

Dental casts of 43 consecutively treated Caucasian patients with a complete UCLP and who were treated at the Nijmegen Cleft Palate Center were included to compare with Eurocleft. Patients with Simonart's bands and patients with syndromes were excluded. All patients were born between 1976 and 1986 and had to be registered at the Nijmegen Cleft Palate Craniofacial Center within 3 months after birth and before any surgical intervention. Two surgeons operated on all patients. The mean age at which the models were taken was 9 years (range 7.9 to 10.3 years).

In Nijmegen, during the past 19 years, the soft palate is closed at 12 to 14 months of age, whereas the hard palate is left open to be closed at the age of 9 to 11 years together with the bone grafting procedure. The Nijmegen treatment protocol is described in Table 2.1. For patients born before 1985, timing of hard palatal closure was variable. For this study, only patients with a two-stage palate closure with closure of the hard palate after the age of 4 were included.

2.2.2 Methods

The 43 sets of dental casts were categorized by using the GOSLON Yardstick.[11] The anteroposterior relationship is considered to be of the most clinical importance, whereas vertical and transverse relationships are less important and primarily help in ranking borderline cases. In a UCLP case, a score of 1 or 2 means a favorable anteroposterior relationship, which requires no orthodontic treatment or a straightforward orthodontic treatment; a score of 3 means complex orthodontic treatment is required; a score of 4 means a case is at the limits of orthodontic treatment but surgery might be needed; and a score of 5 means a very unfavorable anteroposterior relationship for orthodontic correction that requires orthognatic surgery. Anchor models were available for the GOSLON ratings as a reference to classify dental arch relationships. A duplicate set of the 22 anchor models from the original anchor group representing the five categories of the Yardstick was used in this study.

Duplicate measurement errors were studied on 15 randomly selected cases. These additional cases were randomly ordered among the 43 patients; thus, a total of 58 sets of records were used for assessment. Two Nijmegen observers and two Manchester observers scored the 58 dental casts. The two Manchester observers had also been observers in the Eurocleft study.

Subsequently, the GOSLON scores for the Nijmegen dental arch relationships were compared with the GOSLON outcome of the six-center Eurocleft study.[2] The treatment protocols of these centers can be seen in Table 2.1.

2.2.3 Statistical procedure

Duplicate measurement errors were calculated according to the formula of Dahlberg,[12] and the intraobserver reliability coefficient was calculated as the correlation coefficient. Interobserver agreement for the casts' ratings was calculated on the difference between corresponding measurements, including random errors, systematic differences, reliability coefficients (Pearson correlation coefficients), and proportionally weighted kappa values. The reliability of the overall mean GOSLON score (four observers) was calculated as Cronbach alpha. The Student's t-test was used to compare the treatment outcomes in means of average GOSLON scores between the six Eurocleft centers and Nijmegen. One-way analysis of variance (ANOVA) was used to study the influence of the timing of hard palate closure on the mean GOSLON scores for the Nijmegen patient group.

2.3 Results

2.3.1 Measurement error

Intraobserver agreement on the dental cast rating was high, with a mean reliability coefficient for the four observers of 0.83. A reliability coefficient over 0.7 is generally accepted as sufficient agreement. The duplicate measurement error was only 0.34 GOSLON points.[12]

Table 2.1 *Treatment protocols of the centers A through F (Eurocleft) and Nijmegen (adapted from Shaw et al.[13]).**

	A†	B	C	D	E	F	Nijmegen
Birth	**PSOT Hotz**			**PSOT extra-oral strapping**		**PSOT (T-traction)**	**PSOT (Hotz)**
2-6 mo	Lip closure (Millard, Skoog), 3-4 mo	Lip closure (Tennison) and vomer plasty, 2 mo	Lip closure (variation of methods + timing), within 6 mo	Lip closure (variation of methods + timing), within 6 mo	Lip closure (Millard) and vomer plasty, 3 mo	Lip closure (modified Skoog, Tennison-Randall) and bone grafting, 4-6 mo	Lip closure (Millard), 6-8 mo
9 mo	Soft palate closure (Von Langenbeck, Perko, Wardill, Kriens), 9-15 mo						
12 mo			Palate closure (various methods and timing), 12 mo	Palate closure (various methods and timing), within 2 yr		Palate closure (Veau-Wardill-Kilner), 12 mo	Soft palate closure (modified Von Langenbeck palatoplasty), 12-14 mo
18 mo					Palate closure (modified Von Langenbeck) 18-20 mo		
22 mo		Palate closure (Wardill Pushback), 22 mo					
9 yr	Bone grafting, hard palate closure	Bone grafting	Bone grafting	Bone grafting	Bone grafting	Bone grafting (only in cases with failure of primary bone graft)	Bone grafting and hard palate closure (Von Langenbeck), 9-11 yr (before 1985: variable timing of hard palate closure)

** PSOT: presurgical orthopedic treatment.*
† It must be taken into consideration that center A did not adhere completely to this protocol. Only 31% of the patients received PSOT, in 31% of the patients also periosteoplasty was performed at lip closure and 23% of the patients had one-stage palatal closure around 13 months of age.[14]

The mean GOSLON score for the 4 observers varied between 2.34 and 2.38, indicating the absence of systematic observer influences. The random errors were small, ranging from 0.25 to 0.35. The interobserver agreement for the 4 observers was high, as expressed by reliability coefficients ranging from 0.79 to 0.90 and weighted kappa values ranging from 0.68 to 0.85. The reliability of the overall mean score was 0.96 (Cronbach alpha).

2.3.2 Treatment outcome

Table 2.2 shows the comparison between the Eurocleft centers and the Nijmegen center by using the average of the GOSLON scores (five-point scale). The mean GOSLON score for the Nijmegen center showed a significant difference with the GOSLON outcomes of centers D ($p<.001$), C, and F ($p<.01$), which achieved relatively poor treatment results. The mean GOSLON score of Nijmegen did not significantly differ from the GOSLON scores of Eurocleft centers A, B, and E, which had a relatively better treatment outcome.

Table 2.2 *Comparison of the six Eurocleft centers with the Nijmegen center (N) regarding the mean GOSLON score.*

Center	Number	Mean GOSLON score	Standard deviation	95% Confidence interval for the difference with Nijmegen
N	43	2.36	0.74	
B	27	2.47	0.66	-0.23 to 0.45
E	30	2.59	0.67	-0.13 to 0.59
A	24	2.64	0.64	-0.07 to 0.63
F	19	3.03	0.75	0.26 to 1.08
C	24	3.04	0.87	0.26 to 1.10
D	25	3.46	0.92	0.67 to 1.53

Table 2.3 shows the GOSLON distribution (score 1 to 5) for the Nijmegen center and the six Eurocleft centers. For the Nijmegen group, 9% of the dental arch relationships had a GOSLON score of 1, 52% had a score of 2, 30% had a score of 3, 9% had a score of 4, and no cases had a

score of 5. This means that 61% of the patients had a favorable treatment outcome (scores 1 and 2). Only 9% of the patients (scores 4 and 5) required extensive orthodontic treatment or a combined surgical-orthodontic approach.

Table 2.3 *The GOSLON Yardstick distribution (%) for Nijmegen (N) and the six Eurocleft centers.*

Center	No. of patients	GOSLON score				
		1 (%)	2 (%)	3 (%)	4 (%)	5 (%)
N	43	9	52	30	9	0
B	27	0	60	30	10	0
E	30	4	52	36	8	0
A	24	0	46	45	4	5
F	19	0	31	37	26	6
C	24	5	29	29	32	5
D	25	0	16	35	28	21

The cumulative GOSLON scores per center are presented in Figure 2.1.

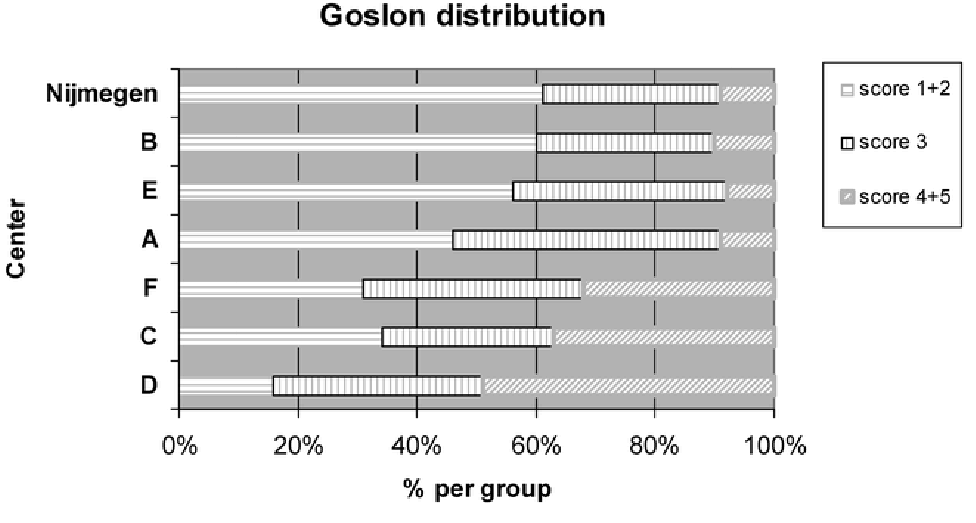


Figure 2.1 *Cumulative GOSLON scores for the Eurocleft centers and Nijmegen. Centers are ordered according to mean GOSLON scores. The horizontal axis shows the combined percentage of GOSLON scores; the vertical axis indicates the center.*

The Nijmegen dental casts could be categorized into three groups according to when the hard palate closure was performed. Hard palate closure was performed at 4 to 7.5 years of age in the first group (n=14), was performed at 7.5 to 10 years of age in the second group (n=9), and was not yet performed when the dental casts were made in the third group (n=20). Concerning the mean GOSLON score, one-way ANOVA showed no significant difference for the three age categories. The mean GOSLON scores were 2.5 (standard deviation [SD]=0.9) for the first patient group, 2.6 (SD=0.5) for the second patient group, and 2.1 (SD=0.7) for the third patient group.

2.4 Discussion

The present study showed that the results obtained with the Nijmegen protocol are comparable with the results of centers A, B, and E in the Eurocleft study. All four centers had highvolume operators, but treatment protocols were not the same.[13] Center A and Nijmegen had rather comparable protocols with delayed closure of the hard palate. However, center A did not adhere completely to its protocol as regards use of presurgical orthopedic treatment (PSOT) (performed in only 31% of the patients), additional use of periosteoplasty at lip closure (in 31% of the patients) and timing of palatal closure (23% had an early one-stage palatal closure).[14] The Nijmegen protocol differed substantially from centers B and E, where no presurgical orthopedic treatment (PSOT) was used and the anterior hard palate closure was performed simultaneously with lip closure at the age of 2 to 3 months by means of a vomer plasty. The remaining palatal cleft was closed between the 18th and 22nd month (Table 2.1).

Of the centers with less favorable outcomes, centers D and F used PSOT. The center F protocol consisted of primary bone grafting together with lip closure at the age of 4 to 6 months and one-stage palatal closure at the age of 12 months. Centers C and D both used a variation of methods and timing in lip closure as well as palatal closure. The relatively disappointing results might have been because of the role of low-volume surgeons in centers C and D and the use of early bone grafting in center F.

For the Nijmegen patient group in the present study, timing of hard palate closure (performed after the age of 4 years) was found to have no significant difference on the mean GOSLON score. On the other hand, Friede and Enemark[8] found in a comparative study that 10- to 16-year-old patients whose hard palates were repaired late had a significant growth advantage in comparison with patients of the same age in whom the hard palate was operated on earlier. However, a disadvantage of late closure of the hard palate could be a negative influence on speech. Although the residual cleft on the hard palate diminishes dramatically during the first year after soft palate closure,[15] a relatively high prevalence of retracted oral articulation (articulation errors where anterior pressure sounds are articulated behind the residual cleft in the hard palate) has been found in children 3 to 7 years of age.[16]

Prudence is in order to reliably interpret the differences in treatment outcome among centers. The inclusion criteria for the Nijmegen patient group did not consist of patients with a Simonart's band; the Eurocleft study did include these patients. This could implicate that the width of the clefts at birth in the Nijmegen patient group was greater than in the Eurocleft groups. Another limiting factor is that the basic growth patterns of different populations are not always the same. In a comparison of Dutch and English children with nonclefts, Trenouth et al.[17] showed that Dutch children were relatively more Angle Class II.

Fundamental limitations of intercenter comparisons are that they cannot distinguish among the influence of different individual elements of a center's protocol on its outcomes or between its protocols and the influence of the personnel who deliver the protocols. Also, even if after a series of intercenter comparisons one or more protocols emerge as highest achievers for treatment outcome, this would be of limited value to the clinical community as a whole, for only protocols can be transferred and not the clinical conditions or the clinicians. The definition of good or bad protocols, or good or bad elements of protocols, requires the explicit arrangements of a randomized clinical trial, preferably performed in an intercenter setting.[18]

It can be concluded from this study that the treatment outcome of the Nijmegen patients with UCLP treated with a two-stage palatal closure, with delayed closure of the hard palate, was comparable with that of the Eurocleft centers with the best outcome. The treatment protocol used in the centers did not have a major influence on the dental arch relationship. Caseload or skill of the surgeon might be more important factors for the quality of the results.

2.5 References

1. Precious DS. The Eurocleft project 1996-2000: overview, discussion. *J Craniomaxillofac Surg*. 2001;29:141-142.
2. Mars M, Asher-McDade C, Brattström V, Dahl E, McWilliam J, Mølsted K, Plint DA, Prahl-Andersen B, Semb G, Shaw WC, The RPS. A six-center international study of treatment outcome in patients with clefts of the lip and palate: part 3. Dental arch relationships. *Cleft Palate Craniofac J*. 1992;29:405-408.
3. Huddart AG. A comparative study of treatment and occlusion in unilateral cleft palate subjects. *Trans Eur Orthod Soc*. 1972;167-176.
4. Semb G. A study of facial growth in patients with unilateral cleft lip and palate treated by the Oslo CLP team. *Cleft Palate Craniofac J*. 1991;28:1-21.
5. Hotz MM, Gnoinski WM. Comprehensive care of cleft lip and palate children at Zürich University: a preliminary report. *Am J Orthod*. 1976;70:481-504.
6. Hotz MM, Gnoinski WM. Effects of early maxillary orthopaedics in coordination with delayed surgery for cleft lip and palate. *J Maxillofac Surg*. 1979;7:201-210.
7. Schweckendiek W. Primary veloplasty: long term results without maxillary deformity. A twenty-five year report. *Cleft Palate J*. 1978;15:268-274.
8. Friede H, Enemark H. Long-term evidence for favorable midfacial growth after delayed hard palate repair in UCLP patients. *Cleft Palate J*. 2001;38:323-329.
9. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Part 5: timing of palate repair. *Cleft Palate J*. 1987;24:54-63.
10. Shaw W, Semb G, Nelson P, Brattström V, Mølsted K, Prahl-Andersen B. The Eurocleft Project 1996-2000. Amsterdam: IOS Press; 2000:270-272.

11. Mars M, Plint DA, Houston WJB, Bergland O, Semb G. The Goslon Yardstick: a new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate J*. 1987;24:314-322.
12. Dahlberg G. Statistical Methods for Medical and Biological Students. New York: Interscience Publications; 1940.
13. Shaw WC, Asher-McDade C, Brattstrøm V, Dahl E, McWilliam J, Mølsted K, Plint DA, Prahl-Andersen B, Semb G, The RPS. A six-center international study of treatment outcome in patients with clefts of the lip and palate: part 1. Principles and study design. *Cleft Palate Craniofac J*. 1992;29:393-397.
14. Semb G. Brattström V, Mølsted K, Prahl-Andersen B, Shaw WC. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 1: introduction and treatment experience. *Cleft Palate Craniofac J*. 2005;42:64-68.
15. Owman-Moll P, Katsaros C, Friede H. Development of the residual cleft in the hard palate after velar repair in a two-stage palatal repair regimen. *J Orofac Orthop*. 1998;59:286-300.
16. Lohmander-Agerskov A. Speech outcome after cleft palate surgery with the Göteborg regimen including delayed hard palate closure. *Scand J Plast Reconstr Hand Surg*. 1998;32:63-80.
17. Trenouth MJ, Davies PHJ, Johnson JS. A statistical comparison of three sets of normative data from which to derive standards for craniofacial measurement. *Eur J Orthod*. 1985;7:193-200.
18. Shaw WC, Brattström V, Mølsted K, Prahl-Andersen B, Roberts CT, Semb G. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 5: discussion and conclusions. *Cleft Palate Craniofac J*. 2005;42:93-98.

Chapter 3

Treatment outcome in unilateral cleft lip and palate evaluated with the GOSLON Yardstick: A meta-analysis of 1236 patients

Pieter JPM Nollet
Christos Katsaros
Martin A van 't Hof
Anne Marie Kuijpers-Jagtman

Plast Reconstr Surg 2005;116:1255-1262

Summary

Background: The goal of this study was to assess determinants for treatment outcome in unilateral cleft lip and palate, evaluated according to the Great Ormond Street London and Oslo (GOSLON) Yardstick and 5-year-index ratings by means of a meta-analysis.
Methods: Multiple databases were searched for publications in which patient groups were evaluated by GOSLON ranking or the GOSLON-like 5-year index. From the 15 selected publications, the following background variables could be extracted and were evaluated as determinants for treatment outcome in unilateral cleft lip and palate: year of birth, average age of the patient at the time of GOSLON classification, racial background, presence of Simonart's band, infant orthopedics, palatal closure before the age of 3 versus palatal closure at a later age, bone graft, and number of surgeons.
Results: The total number of patients included in the meta-analysis was 1236. Patients whose soft and hard palate were closed before the age of 3 presented significantly poorer ($p=0.003$) GOSLON scores (mean score, 2.9; SD 0.4) than patients whose palate was closed at a later age (mean GOSLON score, 2.3; SD 0.2).
Conclusions: Delayed palatal closure generally results in better dental arch relationships than early palatal closure. Well-designed, randomized clinical trials are required for further investigation of the optimal timing for palatal closure.

3.1 Introduction

Evaluation of treatment outcome is essential to allow for identification and implementation of the highest possible standards of care. However, the range of outcome of the treatment of cleft lip and palate can be considerable. Differences in treatment results may be related to variation in the sequence, timing, and technique of treatment, the organization and delivery of care, as well as in the skills and experience of individual surgeons. State-of-the-art reviews consistently indicate that few centers, if any, use the same approach in surgical technique, timing, or sequence, not to mention the variety of ancillary interventions, like infant orthopedics, orthodontics, speech therapy, and secondary operations.[1] Of the 201 centers that are registered in Eurocleft, 194 have different treatment protocols for unilateral clefts.[2] With such controversy and confusion, clinicians face the impossible task of selecting the optimal delivery of care that offers the best overall chance of success for their patients.

Facial growth is one of the key areas of interest for the quality of cleft treatment outcome. Good facial growth may result in dental arch relationships that can be treated conventionally, avoiding surgical correction of the skeletal bases, and, thus, provide optimal results in terms of facial appearance.[3] Several methods for rating dental arch relationships in patients with unilateral cleft lip and palate have been described. A method that became quite popular in past decades is the Great Ormond Street London and Oslo Yardstick (GOSLON).[4] The GOSLON Yardstick assesses dental arch relationship in terms of anteroposterior, transverse, and vertical discrepancies in persons with unilateral cleft lip and palate. The assessment includes the ranking of casts into one of five categories compared to a standard set of casts reflecting the different categories. A very good dental arch relationship is scored as one; a very poor relationship is scored as five. The GOSLON Yardstick has been successfully used in studies assessing treatment outcome in children with unilateral cleft lip and palate and proved to be capable of discriminating the quality of the dental arch relationships among different centers.[4,5] This makes the GOSLON Yardstick a useful tool for comparative cross-center studies.

Although the application of the GOSLON Yardstick also proved to be reliable for the deciduous dentition,[6] later on a new rating system was developed for the deciduous dentition.[7] This "GOSLON-type" index was specifically developed for children with unilateral cleft lip and palate at the age of 5, but is comparable to the GOSLON Yardstick; it includes a similar ranking system with five categories and a similar use of reference models. The 5-year-old index has shown to be a suitable tool for assessing treatment outcome in the primary dentition and proved to be useful in intercenter comparisons.[8-10]

A meta-analysis of the literature (i.e., a statistical analysis of summary results across a group of studies with common underlying characteristics) allows comparison of outcome of cleft surgery together with other major components of cleft care. In addition, multicenter comparison increases the number of patients examined, which facilitates more powerful statistics and enhances reliable conclusions. Therefore, the goal of this study was to assess determinants for treatment outcome in unilateral cleft lip and palate according to GOSLON and 5-year-index ratings by means of a meta-analysis.

3.2 Patients and methods

3.2.1 Data sources

In December of 2003, the Cochrane databases (the Database of Abstracts of Reviews of Effects and the Cochrane Central Register of Controlled Trials) and the Medline database were searched. In addition, an Internet search with multiple databases was performed, using the combined databases of Medline, Current Contents Archives, Biological Abstracts, and Cinahl. The Medline search, as well as the search with multiple databases, is described in Table 3.1. Within the group of underlined hits, 48 articles were unique and subsequently manually evaluated for inclusion in the meta-analysis. The hits retrieved by queries 4, 6, and 7 from the Medline search and by 1, 4, and 5 from the multiple database search yielded 48 unique articles, which mentioned the GOSLON Yardstick and/or the 5-year-old index. Subsequently, two more recent articles[11,12] that presented GOSLON data from our own department were added for data selection.

Table 3.1 *Medline search and multiple database search (databases of Medline, Current Contents Archives, Biological Abstracts and CINAHL combined) from the year 1966 through December 2003.*

Search database(s)	**Search No.**	**Search criteria**	**No publications found***
Medline	1	"Cleft-Palate" (all subheadings in MIME, MJME)	10,609
	2	"UCLP"	171
	3	Search No. 1 or 2	10,625
	4	"GOSLON" or "goslon"	12
	5	"Jaw-Relation-Record" in MIME, MJME	2907
	6	Search Nos. 3 and 5	24
	7	"5 year index" or "5-year-old index"	17
Medline, Current Contents Archives, Biological Abstracts, and Cinahl			
	1	"Goslon" or "GOSLON"	21
	2	Dental arch relationship	70
	3	"UCLP" or "unilateral cleft lip and palate"	1034
	4	"UCLP" or "unilateral cleft lip and palate" and "dental arch relationship"	33
	5	"5 year index" or "5-year-old index"	32

3.2.2 Data selection

Criterion for including an article in the meta-analysis was the presence of one or more groups of unilateral cleft lip and palate patients, which were categorized using the GOSLON Yardstick and/or the 5-year-old index. The distribution of the GOSLON and/or 5-year-old index scores should be present. Two researchers (Nollet and Kuijpers-Jagtman) independently carried out the screening of the 50 articles based on the abstracts of the retrieved publications. Screening of the abstracts yielded 19 articles that met the inclusion criterion. A few publications presented GOSLON data for patients who also were used in one of the other 19 publications. In such a case, the publication with the largest number of patients was selected. Therefore, the study of Nollet et al.[12] that included 49 patients was excluded in favor of the publication of Noverraz et al.,[6] which included 68 patients. The article of Johnson et al.[13] reported GOSLON scores on 49 patients and was excluded in favor of the publication of Johnson et al.,[14] which comprised 54 patients. One publication[10] reported GOSLON scores of patients previously reported in the Clinical Standards Advisory Group study[15] and was therefore excluded. One publication[7] was excluded because it presented only GOSLON score 4 and 5 whereas another publication[8] on the same patients presented the GOSLON distribution 1 through 5. Finally, a total of 15 articles could be included in the meta-analysis without additional exclusion criteria. All selected articles are listed in Table 3.2.[3-6,8,9,12,14,16-22] The reference lists of the included articles were hand searched and references to related articles were followed-up, which did not yield additional articles. This could have been expected since the GOSLON and 5-year-index classification methods date from 1987 and 1997 respectively, when registration of publications in databases was already in full operation.

3.2.3 Data extraction

The article by Williams et al.[19] presented GOSLON data on two independent patient groups of which one patient group needed to be excluded since the GOSLON data for these patients were previously presented in a publication by Johnson et al.[14] The article of Pigott et al.[20] reported GOSLON scores on three independent patient groups of which one patient group needed to be excluded since the article of Hathorn et al.[3] formerly published the GOSLON distribution for these patients. Finally, 27 independent patient groups were examined, which are all presented in Table 3.2, together with the number of patients for each group.

For this study, the GOSLON Yardstick and the 5-year-old index were considered to be equivalent as an expression tool of treatment outcome in unilateral cleft lip and palate. For each patient group, the mean GOSLON score as well as the combined percentage of GOSLON scores 1 and 2, GOSLON score 3, and the combined percentage of GOSLON scores 4 and 5 were extracted. Several publications reported on patient groups, which were submitted to GOSLON classification at different ages. Then, the GOSLON scores closest to 9 years of age for the GOSLON ranking and closest to 5 years of age for the 5-year-index were taken for further analysis.

Table 3.2 *List of the 15 included papers with the number of patients for each examined patient group.*

Article No.	Reference No.*/ first author	Year of publication	Independent patient group	Origin of patient group	No. of patients
1	4/Mars	1987	A	NO	55
			B	UK	30†
			C	UK	30†
2	5/Mars	1992	A	DK, NL, NO, SE, UK (2 groups)‡	24
			B		27
			C		24
			D		25
			E		30
			F		19
3	6/Noverraz	1993	A	NL	68
4	3/Hathorn	1996	A	UK	32
5	8/Atack	1998	A	UK	46
			B	NO	54
6	16/Leonard	1998	A	UK	25
7	14/Johnson	2000	A	AU	54
8	17/Morris	2000	A	UK	35
9	18/Williams	2001	A	UK	223
			B	UK	229
10	19/Williams	2001	A	AU	18
11	9/DiBiase	2002	A	UK	44
12	20/Pigott	2002	A	UK	19
			B	UK	19
13	21/Chan	2003	A	US	19
			B	US	21
14	22/Choudhary	2003	A	UK	25
15	11/Bongaarts	2004	A	NL	20
			B	NL	21

NO, Norway; UK, United Kingdom; DK, Denmark; NL, Netherlands; SE, Sweden; AU, Austria; US, United States.
*Reference No. corresponds with the reference number in the reference list of this article.
†Estimated sample size.
‡The article does not mention which patient group corresponds to which country of origin.

The following background variables could be extracted from most of the patient groups and were considered as possible determinants for treatment outcome in unilateral cleft lip and palate:

- Year of birth (mean birth year before/after 1985)
- Average age of the patient group at the time of GOSLON classification (mean age, 4 to 7 years and 8 to 12 years)
- Racial background (100% Caucasian yes/no)
- Inclusion of patients with a Simonart's band (yes/no)
- Infant orthopedics (yes/no)
- Palatal closure before the age of 3 years versus palatal closure at a later age (early/delayed palatal closure)
- Bone graft (for no patients/for some patients/for all patients)
- Number of surgeons operating on the considered cleft group (≤3 surgeons/> 3 surgeons)

Two independent researchers (Nollet and Katsaros) extracted all data for every patient group. Data were retrieved from Tables, Figures, and text in the publications. In a few cases of disagreement, a third experienced researcher (Kuijpers-Jagtman) was asked for her opinion and consensus was reached.

3.2.4 Statistical analysis

The influence of the eight background variables on the two outcome variables, the mean GOSLON scores, as well as the combined percentage of GOSLON scores 4 and 5, was studied and t-tests were applied.

In publications where the mean GOSLON score was not presented, the mean was calculated from the frequency distribution of the scores 1 to 5. In five publications without a specified mean, the full distribution of the GOSLON scores was not given, but only the frequencies of the combinations 1+2, 3, 4+5. Here, the mean was calculated after splitting up the categories 1+2 and 4+5 proportionally to the distribution in the other studies.

Multiple regression (weighted according to sample sizes) was applied to find combined influences of the background variables on the GOSLON outcome. To prevent too much multiple testing, the outcome was restricted to two variables, i.e., mean GOSLON score and the combined percentage of GOSLON score 4 and 5. For the two patient groups (see Table 3.2) where no sample size was specified, the regression weights were set to a modest large sample size of 30. Due to many missing values not reported in the original publications, a full multiple regression could not be carried out. The analysis had to be restricted to the influence of only two determinants at the same time.

Table 3.3 *Description of categories for the considered determinants of treatment outcome in unilateral cleft lip and palate.*

Determinants for treatment outcome	**Description of categories for each determinant**	**No. patient groups***	**GOSLON Mean ± SD**		**Percent GOSLON 4 and 5 Mean ± SD**	
Birth period	1= mean birth year < 1985	17	2.9 ± 0.4	NS†	30 ± 18	NS†
	2= mean birth year > 1985	10	2.8 ± 0.4		23 ± 15	
Patient age	1= mean age between 4-7 yrs	9	2.7 ± 0.4	NS†	21 ± 16	NS†
	2= mean age between 8-12 yrs	18	3.0 ± 0.4		31 ± 17	
Racial background	1= Caucasian patients only	4	3.0 ± 0.3	NS†	29 ± 11	NS†
	2= Non-Caucasians included	13	2.8 ± 0.4		23 ± 18	
Simonart's band patients	1= Simonart's band included	3	2.2 ± 0.1	0.001†	2 ± 3	0.009†
	2= Simonart's band excluded	13	2.9 ± 0.3		26 ± 13	
Infant orthopedics	1= No patients had infant orthopedics	11	2.9 ± 0.5	NS†	28 ± 18	NS†
	2= Some patients had infant orthopedics	12	2.9 ± 0.5		26 ± 17	
Palatal closure (soft and hard)	1= early closure (age < 3 yrs)	19	2.9 ± 0.4	0.003†	29 ± 14	0.002†
	2= delayed closure (age > 3 yrs)	4	2.3 ± 0.2		4 ± 4	
Bone graft	0= for no patients	8	2.7 ± 0.5	NS‡	23 ± 18	NS‡
	1= for some patients	5	2.9 ± 0.5		27 ± 20	
	2= for all patients	7	2.8 ± 0.4		25 ± 16	
No. of surgeons	1= 1, 2 or 3 surgeons	10	2.8 ± 0.5	NS†	26 ± 18	NS†
	2= more than 3 surgeons	14	2.9 ± 0.4		28 ± 18	

NS, not significant (p>0.05).
*The maximum possible number of patient groups per determinant is 27.
†p-values for t-tests on mean GOSLON score and combined percent GOSLON score 4 and 5.
‡No significant influence as tested by one-way Anova.

3.3 Results

The total number of patients included in the meta-analysis was 1236 (number of patients per group range, 18 to 229, Table 3.2). Table 3.3 presents the effects of the studied determinants for mean GOSLON score and combined percentage of GOSLON score 4 and 5. The studies with a delayed palatal closure (>3 years) gave significantly better mean GOSLON scores and a lower percentage of cases in the combined GOSLON category 4 and 5 (p=0.003). Also, inclusion of patients with a Simonart's band in the unilateral cleft lip and palate group gave better GOSLON scores and a lower percentage of cases were considered in need of surgery (p=0.009). The timing of palatal closure and the presence of a Simonart's band were highly correlated in the considered publications (r=0.83). This led to collinearity and the influence of palatal closure and presence of a Simonart's band could not be separated by statistical analysis. As palatal closure is performed in every patient, while only a few patients will have a Simonart's band, the influence of the timing of palatal closure was considered to be a stronger determinant and was, therefore, used in a second step of multiple regression. Each background variable was entered together with the palatal surgery timing to find additional influences. None of the other background variables showed a significant relationship with the GOSLON score (all variables p>0.15).

Thus, the only interpretable influence observed from this meta-analysis is given by the timing of palatal closure. The difference between early and late palatal closure for the mean GOSLON score is 0.64 and for the combined percentage of GOSLON score 4 and 5 is 26 percent. These effects are represented in Table 3.4.

Table 3.4 *The effect of early versus delayed palatal closure.*

	Early palate closure (n = 19 groups)	**Delayed palate closure (n = 4 groups)**	**Closure effect (difference = regression coefficient)**	**95% CI for closure effect (weighted)**	**p-value***
Mean GOSLON score	2.9 (SD = 0.4)	2.3 (SD = 0.2)	0.64 (SE = 0.18)	0.28-1.00	0.002
Percentage GOSLON score 4 and 5	29 (SD = 14)	4 (SD = 4)	26 (SE = 7)	12-40	0.002

* p-value from weighted regression.

3.4 Discussion

Cleft lip and palate care involves several anatomical structures and can affect a variety of functions, including speech, hearing, and social interaction.[18] To evaluate the total outcome of cleft care, a wide range of outcomes needs to be measured, although it is sometimes difficult to judge the effect of one area of treatment without taking into account its influence on other aspects of growth and development. In this study, the evaluation of treatment outcome in unilateral cleft lip and palate was restricted to judging dental arch relationships because dental arch relationships are essential parameters for facial growth and, thus, are an important indicator for the quality of cleft treatment outcome. Good facial growth may result in dental arch relationships that can be treated orthodontically without a need for surgical correction of the skeletal bases.[3]

In the considered publications, the GOSLON Yardstick was used to assess dental arch relationships. The way of presenting GOSLON scores in literature is rather inconsistent and complicates reliable comparisons of different patient groups. Some publications do not report the full GOSLON distribution but only mention GOSLON combinations 1+2, 3, 4+5, whereas for other patient groups only GOSLON percentages for every GOSLON score are mentioned without the total number of patients examined.[4] To facilitate intercenter comparison and evaluation, a consistent way of presenting GOSLON scores is recommended. The full GOSLON distribution in percentages for all five categories should be presented, together with the mean GOSLON score with SD and the total number of patients examined. It is not advocated to present combined percentages of GOSLON scores since the GOSLON Yardstick was introduced as a categorization method into five categories and is sometimes considered rather coarse and incapable of distinguishing the finer differences in the severity of malocclusions.[4,5] Combining percentages of GOSLON scores would even enhance the roughness of the GOSLON classification.

All the patient groups considered for selection in this meta-analysis were scrutinized for GOSLON scores of patients previously reported in other publications. In case publications including GOSLON scores of patients from another article, the patient group with the largest number of patients was selected for further analysis. The British Clinical Standards Advisory Group study[18] reported on 12-year-old patients from 50 centers throughout the United Kingdom who were born between April 1, 1982, and March 31, 1984, and 5-year-old patients born between April 1, 1989, and March 31, 1991. This could imply that there is an overlap for the Clinical Standards Advisory Group study with some of the other studied patient groups from the United Kingdom. However, since all other studied British patient groups in this meta-analysis have a range of birth years that is greater than 2 years and the data of the patients in the Clinical Standards Advisory Group study were collected from 50 centers throughout the United Kingdom, the overlap is too small to be considered relevant for this meta-analysis.

The results from this meta-analysis suggest that apart from the timing of palatal surgery, there were no background variables that had an effect on the dental arch relationships in unilateral cleft lip and palate. However, inadequate reporting for some of the considered determinants, (i.e. race of the patients, number of patients with a preexisting Simonart’s band, number of patients who underwent bone grafting, and number of surgeons involved) hampered the statistical analysis of earlier data. Consequent and explicit reporting of the number of patients undergoing the intervention examined would facilitate reliable intercenter comparisons and remote cleft audit.

Patients with a Simonart’s band were sometimes included and sometimes excluded in the studied publications. However, the preoperative cleft width is generally smaller for patients with a Simonart’s band. This implicates that the positive effect of primary surgery and, thereby, the influence on treatment outcome could be overvalued for studies including patients with Simonart’s band. Therefore, it is recommended for future cleft studies that Simonart’s band patients be excluded or analyzed separately.

The main finding from this study is that delayed palatal closure generally has better treatment outcome regarding dental arch relationships than early palatal closure. For many years there has been much controversy about the timing of palatal closure. Some investigators advocated early hard palate closure,[23,24] while others suggested that delayed hard palate closure would result in more favorable growth of the maxilla.[25-28] The variety of timing of palatal closure was also shown in the Eurocleft Project, 1996 to 2000. The timing of independently performed soft palate closures varied from birth to 3 years of age, the timing of independently performed hard palate closure varied from birth to 13 years of age, and the timing of hard and soft palate closure when performed simultaneously varied from 3 months to 3 years of age.[29] A disadvantage of late closure of the hard palate could be a negative influence on speech. Although the residual cleft on the hard palate diminishes dramatically during the first year after surgery,[30] a relatively high prevalence of retracted oral articulation has been found in children 3 to 7 years of age.[31]

Other considered determinants for treatment outcome in cleft lip and palate in this study could not be established. The number of surgeons was not found to be a determinant for treatment outcome, although intercenter studies in the past have demonstrated that factors that influence treatment outcome include patient load as an indicator for experience of the operating surgeon and the organization of services.[1,15]

The purpose of a meta-analysis is to objectively retrieve information from publications that study the same topic and to combine these data to get an overall result. The considered publications in this meta-analysis are all observational studies with the exception of a randomized controlled clinical trial.[11] Randomized controlled clinical trials are generally accepted as the preferred research design mainly because conceptually it is easier to attribute any observed effect to the treatments being compared. However, a recent study[32] that compared individual randomized controlled clinical trials with observational studies in 19 therapeutic areas and another study[33] that compared meta-analyses of randomized controlled clinical trials with meta-analyses of cohort and case-control studies in five therapeutic areas found no major differences between the estimates of treatment effects in observational studies and randomized controlled clinical trials. Although the confounding factors that may distort the results in observational research are evident, observational studies have several advantages over randomized controlled clinical trials, including lower cost, longer time frame, and a broader range of patients.[34] In addition, observational studies can generate risk factors, prognostic indicators, and treatment outcomes that should be evaluated in a randomized controlled clinical trial; thereby, observational studies could help in conducting the set up of the randomized controlled clinical trial, e.g., with the determination of the type of intervention to be examined and the estimation for the SD in the calculation of the required sample size of treatment groups. Based on the results of the present meta-analysis, there is reason to opt for a randomized controlled clinical trial in early versus delayed palatal closure. At the moment, this question is incorporated in the Scandcleft project,[35] a multicenter randomized controlled trial of primary cleft lip and palate surgery. This ongoing study is performed as a collaboration among 10 Scandinavian and British centers to elucidate the best timing and technique of primary surgery in unilateral cleft lip and palate. Future randomized controlled clinical trials like Scandcleft can define the quality of different protocols, or elements of protocols, and thereby improve treatment outcome in unilateral cleft lip and palate.

3.5 References

1. Shaw, WC, Asher-McDade, C, Brattström, V, et al. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 1. Principles and study design. *Cleft Palate Craniofac J.* 1992;20:393-397.
2. Shaw, WC, Semb, G, Nelson, P, et al. The Eurocleft Project 1996-2000: Overview. *J Craniomaxillofac Surg.* 2001;29:131-140.
3. Hathorn, I, Roberts-Harry, D, Mars, M. The GOSLON Yardstick applied to a consecutive series of patients with unilateral clefts of the lip and palate. *Cleft Palate Craniofac J.* 1996;33:494-496.
4. Mars, M, Plint, DA, Houston, JB, Bergland, O, Semb, G. The GOSLON yardstick: A new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate Craniofac J.* 1987;24:314-322.

5. Mars, M, Asher-McDade, C, Brattström, V, et al. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 3. Dental arch relationships. *Cleft Palate Craniofac J*. 1992;29:405-408.
6. Noverraz, AEM, Kuijpers-Jagtman, AM, Mars, M, Van 't Hof, MA. Timing of hard palate closure and dental arch relationships in unilateral cleft lip and palate patients: A mixed-longitudinal study. *Cleft Palate Craniofac J.* 1993;30:391-396.
7. Atack, NE, Hathorn, I, Semb, G, Dowell, T, Sandy, JR. A new index for assessing surgical outcome in unilateral cleft lip and palate subjects aged five: Reproducibility and validity. *Cleft Palate Craniofac J.* 1997;34:242-246.
8. Atack, NE, Hathorn, I, Dowell, T, Sandy, J, Semb, G, Leach, A. Early detection of differences in surgical outcome for cleft lip and palate. *Br J Orthod.* 1998;25:181-185.
9. DiBiase, AT, DiBiase, DD, Hay, NJ, Sommerlad, BC. The relationship between arch dimensions and the 5-year index in the primary dentition of patients with complete UCLP. *Cleft Palate Craniofac J*. 2002;39:635-640.
10. Williams, AC, Sandy, RS. Risk factors for poor dental arch relationships in young children born with unilateral cleft lip and palate. *Plast Reconstr Surg*. 2003;111:586-593.
11. Bongaarts, CAM, Kuijpers-Jagtman, AM, Van 't Hof, MA, Prahl-Andersen, B. The effect of infant orthopedics on the occlusion of the deciduous dentition in children with complete unilateral cleft lip and palate (Dutchcleft). *Cleft Palate Craniofac J*. 2004;41:633-641.
12. Nollet, PJPM, Katsaros, C, Van 't Hof, MA, et al. Photographs of study casts: An alternative medium for rating dental arch relationships in unilateral cleft lip and palate. *Cleft Palate Craniofac J.* 2004;41:646-650.
13. Johnson, N, Williams, A, Singer, S, Southall, P, Sandy, J. Initial cleft size does not correlate with outcome in unilateral cleft lip and palate. *Eur J Orthod*. 2000;22:93-100.
14. Johnson, N, Williams, AC, Singer, S, Southall, P, Atack, N, Sandy, JR. Dentoalveolar relations in children born with a unilateral cleft lip and palate (UCLP) in Western Australia. *Cleft Palate Craniofac J.* 2000;37:12-16.
15. Sandy, JR, Williams, AC, Mildinhall, S, et al. The Clinical Standards Advisory Group (CSAG) cleft lip and palate study. *Br J Orthod*. 1998;25:21-30.
16. Leonard, AG, Kneafsey, B, McKenna, S, et al. A retrospective comparison of craniofacial form in Northern Irish children with unilateral cleft lip and palate. *Cleft Palate Craniofac J*. 1998;35:402-407.

17. Morris, DO, Roberts-Harry, D, Mars, M. Dental arch relationships in Yorkshire children with unilateral cleft lip and palate. *Cleft Palate Craniofac J*. 2000;37:453-462.
18. Williams, AC, Bearn, D, Mildinhall, S, et al. Cleft lip and palate care in the United Kingdom. The clinical Standards Advisory Group (CSAG) Study. Part 2: Dentofacial outcomes and patient satisfaction. *Cleft Palate Craniofac J*. 2001;38:24-29.
19. Williams, AC, Hohnson, NC, Singer, S, et al. Outcomes of cleft care in Western Australia: A pilot study. *Aust Dent J*. 2001;46:32-36.
20. Pigott, RW, Albery, EH, Phil, M, et al. A comparison of three methods of repairing the hard palate. *Cleft Palate Craniofac J*. 2002;39:383-391.
21. Chan, KT, Hayes, C, Shusterman, S, Mulliken, JB, Will, LA. The effects of active infant orthopedics on occlusal relationships in unilateral cleft lip and palate. *Cleft Palate Craniofac J*. 2003;40:511-517.
22. Choudhary, S, Cadier, MAM, Shinn, DL, Shekhar, K, McDowall, RAW. Effect of Veau-Wardill-Kilner type of cleft palate repair on long-term midfacial growth. *Plast Reconstr Surg*. 2003;111:576-582.
23. Huddart, AG. A comparative study of treatment and occlusion in unilateral cleft palate subjects. *Trans Eur Orthod Soc*. 1972;167-176.
24. Semb, G. A study of facial growth in patients with unilateral cleft lip and palate treated by the Oslo CLP team. *Cleft Palate Craniofac J*. 1991;28:1-21.
25. Hotz, MM, Gnoinski, WM. Comprehensive care of cleft lip and palate children at Zürich University: A preliminary report. *Am J Orthod*. 1976;70:481-504.
26. Schweckendiek, W. Primary veloplasty: Long-term results without maxillary deformity. A twenty-five-year report. *Cleft Palate Craniofac J*. 1978;15:268-274.
27. Hotz, MM, Gnoinski, WM. Effects of early maxillary orthopaedics in coordination with delayed surgery for cleft lip and palate. *J Maxillofac Surg*. 1979;7:201-210.
28. Friede, H, Enemark, H. Long-term evidence for favorable midfacial growth after delayed hard palate repair in UCLP patients. *Cleft Palate Craniofac J*. 2001;38:323-329.
29. Shaw, WC, Semb, G, Nelson, P, Mølsted K, Prahl-Andersen B. The Eurocleft Project 1996-2000. Amsterdam: IOS Press; 2000:270-272.
30. Owman-Moll, P, Katsaros, C, Friede, H. Development of the residual cleft in the hard palate after velar repair in a two-stage palatal repair regimen. *J Orofac Orthop*. 1998;59:286-300.

31. Lohmander-Agerskov, A. Speech outcome after cleft palate surgery with the Göteborg regimen including delayed hard palate closure. *Scand J Plast Reconstr Hand Surg*. 1998;32:63-80.
32. Benson, K, Hartz, AJ. A comparison of observational and randomized controlled trials. *N Engl J Med*. 2000;342:1878-1886.
33. Concato, J, Shah, N, Horwitz, RI. Randomized, controlled trials, observational studies and the hierarchy of research designs. *N Engl J Med*. 2000;342:1887-1892.
34. Feinstein, AR. Epidemiologic analyses of causation: The unlearned scientific lessons of randomized trials. *J Clin Epidemiol*. 1989;42:481-489.
35. Semb, G. Multicenter trials in cleft lip and palate surgery. Presented at the International Collaboration on Craniofacial Anomalies, World Health Organization, Geneva, Switzerland, March 5-8, 2000.

Chapter 4

Photographs of study casts: An alternative medium for rating dental arch relationships in unilateral cleft lip and palate

Pieter JPM, Nollet
Christos Katsaros
Martin A van 't Hof
Catharina AM Bongaarts
Gunvor Semb
William C Shaw
Anne Marie Kuijpers-Jagtman

Cleft Palate Craniofac J. 2004;41:646-650

Summary

Objective: To investigate the reliability of using photographs of study casts as an alternative to casts for rating dental arch relationships.
Design: Repeated-measures study.
Setting: Cleft Palate Center of the University Medical Center Nijmegen, Nijmegen, The Netherlands.
Patients: Records of children with complete unilateral cleft lip and palate (UCLP) (n=49) at the age of 9 years were included.
Mean outcome measures: Statistics of intra- and interexaminer agreement.
Results: No significant differences were found between the rating of dental casts and photographs of dental casts, using the GOSLON Yardstick.
Conclusions: Photographs of dental casts provide a consistent, reproducible method for rating dental arch relationships in patients with UCLP at the age of 9 years and provide a reliable alternative to the application of the GOSLON Yardstick on dental casts.

4.1 Introduction

Evaluating and comparing dental arch relationships in patients with cleft lip and palate requires a reliable method of rating. Several methods for rating dental arch relationships in patients with unilateral cleft lip and palate (UCLP) have been described. Most methods score the presence or absence of crossbite[1-4] or the amount of overjet and overbite and the sagittal molar occlusion.[3,5] A method that became quite popular in the past decades is the GOSLON (Great Ormond Street London and Oslo) Yardstick.[6] The GOSLON Yardstick is a rating system specifically developed to grade dental arch relationships in the late mixed and/or early permanent dentition in children with UCLP into five categories. The GOSLON Yardstick has been successfully used in studies assessing treatment outcome in children with UCLP.[6,7] In addition, the GOSLON Yardstick has proved to be capable of discriminating the quality of the dental arch relationships between different centers.[8] This makes the GOSLON Yardstick a useful tool for comparative cross-center studies.

However, for intercenter studies or studies that require ratings by external judges, the judges, the casts, or both must travel to the place at which rating will be carried out. This inevitably is associated with some expense, inconvenience, and possible damage to the plaster casts.

A more convenient approach would be to substitute the casts by photographs of the casts. Indeed a scoring method that could be performed over the Internet would be the most cost effective.

The purpose of this study was to investigate the reliability of rating dental arch relationships using photographs instead of study casts, both for the test cases and the reference set.

4.2 Subjects and methods

Records of 49 consecutive patients with a complete UCLP born between 1976 and 1986 and treated at the Nijmegen Cleft Palate Center were used to test the photograph method. Patients with Simonart’s bands or syndromes as well as non-Caucasian patients were excluded. All patients had to be registered at the Nijmegen Cleft Palate Center within 3 months after birth and before any surgical intervention. A set of dental casts around the age of 9 years (range 7.9 to 10.3 years) was available for all patients.

Dental arch relationships were rated with the GOSLON Yardstick on a 5-point-scale.[6] A score of 1 or 2 means a favorable anteroposterior relationship that requires no orthodontic treatment or a straightforward orthodontic treatment (e.g., Class II division 1 and Class I dental relationships, respectively); patients with score 3 require complex orthodontic treatment (usually an anterior end-to-end situation); patients with score 4 are at the limits of orthodontic treatment but surgery might be needed; a score of 5 means a very unfavorable anteroposterior relationship for orthodontic correction and requires orthognathic surgery (for example, a severe mesio-occlusion with osteotomy necessary for correction). Reference models are available for each GOSLON score as a guide to assist reproducible rating. A duplicate set of the 22 reference models from the original reference group representing the five categories of the Yardstick was used to categorize the dental casts.

For the GOSLON classification with photographs, digital images of the 22 reference models were obtained with a Nikon (Melville, NY) D1 camera and an AF Micro Nikkor (Melville, NY) 60-mm/1:2.8 D lens. The lens-object distance was about 30 cm. For each set of reference models, a frontal view, views from the right and left side, and occlusal views of the upper and lower arch were made with a black background. The time needed for photographing one set of models took no more than 5 minutes. The five views of each anchor model were put into a row on a PowerPoint slide (Microsoft Corp., Redmond, WA); the 22 different reference cases were ordered in sequence from GOSLON score 1 to 5. The observers were asked to print the images of the reference models to assist the rating of the 49 cases.

The photographs of the 49 dental casts of the UCLP sample were made with the same camera as used for the reference models. The pictures were loaded into PowerPoint, and each slide contained five views of one set of the dental casts of one patient together with the identifying case number (Figure 4.1). Each judge viewed the patients as a PowerPoint file on a CD using his or her own laptop computer.

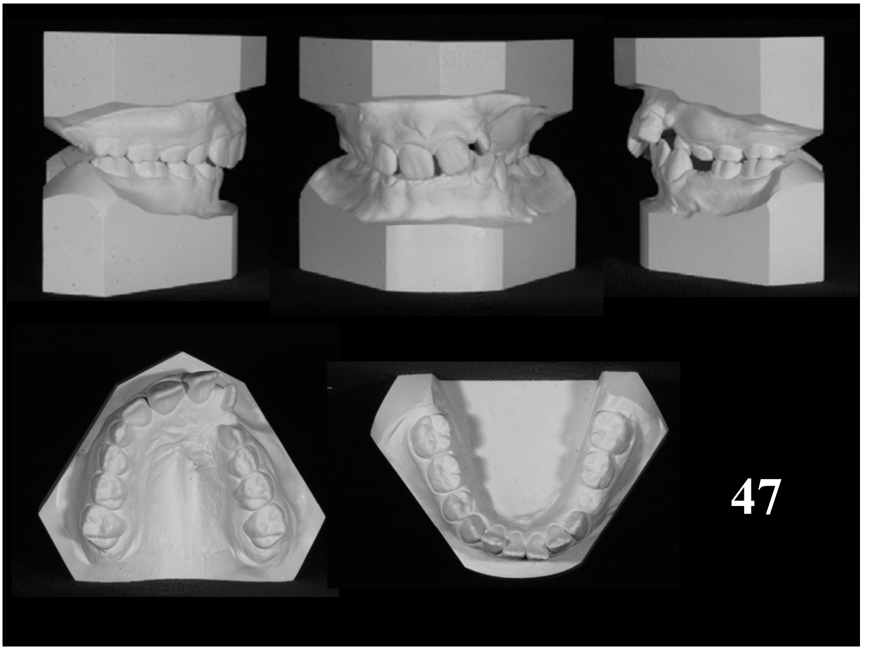


Figure 4.1 *Five views of one set of dental casts for patient 47.*

Duplicate measurement errors were studied on 15 randomly selected subjects. These additional subjects were randomly ordered among the 49 patients; thus, a total of 64 sets of records were used for assessment. The dental casts as well as their corresponding photographs were scored independently by four observers (C.B., B.S., G.S., A.K.). The casts were rated first; 2 days later the photographs were rated.

For the GOSLON scores, means and SDs per observer were calculated, and the range of means and SDs were tabulated. Duplicate measurement errors were calculated according to Dahlberg's[9] formula, and the reliability coefficient was calculated as the correlation coefficient. Interobserver agreement for casts and pictures and intraobserver agreement on casts versus pictures were calculated on the difference between corresponding measurements including: systematic differences, random errors, reliability coefficients (Pearson correlation coefficients), and proportionally weighted kappa values.

4.3 Results

The mean GOSLON scores of the 49 patients, depending on the four observers and the method (casts/photographs), varied from 2.29 to 2.33 (SD 0.74 to 0.83).

4.3.1 Duplicate measurements

Intraobserver agreement was calculated as agreement on casts and agreement on photographs. As shown in Table 4.1, both agreement measures were high with a mean reliability coefficient for the four observers of 0.83 for the dental casts and 0.87 for the pictures. A reliability coefficient over 0.7 is generally accepted as sufficient agreement. The duplicate errors were small: only 0.34 GOSLON points for the dental casts and 0.30 GOSLON points for the pictures (Table 4.1).

Table 4.1 *Mean Intraobserver Agreement Statistics.**

Agreement statistics	Agreement on casts	Agreement on photographs
Duplicate error (GOSLON points)	0.34	0.30
Reliability coefficient	0.83	0.87

* Included four observers on 15 patients. Duplicate errors were calculated by Dahlberg's formula and the reliability coefficients as Pearson correlation coefficients.

4.3.2 Interobserver agreement

The interobserver agreement was calculated for the dental casts as well as for the photographs and quantified by systematic differences, random errors, weighted kappa coefficients, and reliability coefficients (Table 4.2). The systematic differences for the dental casts ratings among the four observers were small; the random errors were larger. The interobserver agreement on the cast rating was high to very high, as indicated by weighted kappa values ranging from 0.68 to 0.85. For ordered categorical data, it has been suggested[10] that a kappa value of over 0.6 represents ‘‘good’’ agreement and over 0.8 indicates ‘‘very good’’ strength of agreement. The high interobserver agreement for the dental cast rating is confirmed by reliability coefficients that ranged from 0.82 to 0.90 for the four observers (Table 4.2).

Table 4.2 *Interobserver agreement on casts and photographs.**

	Systematic difference (GOSLON pt)	**Random error (GOSLON pt)**	**Reliability coefficient**	**Weighted kappa**
Dental casts				
A-B	0.04	0.32	0.83	0.74
A-C	0.02	0.34	0.83	0.73
A-D	0.04	0.25	0.90	0.85
B-C	-0.02	0.34	0.82	0.72
B-D	0.00	0.35	0.79	0.68
C-D	0.02	0.27	0.89	0.83
Mean		0.31	0.84	0.76
Photographs				
A-B	0.00	0.33	0.84	0.76
A-C	0.02	0.34	0.83	0.73
A-D	0.02	0.42	0.71	0.57
B-C	0.02	0.34	0.83	0.74
B-D	0.02	0.34	0.82	0.72
C-D	0.00	0.38	0.77	0.65
Mean		0.36	0.80	0.70

* Systematic differences between observer pairs (GOSLON pt), random errors (GOSLON pt), reliability coefficients and weighted kappa values (n=49 cases). A, B, C, D = four different observers.

The systematic differences for the photograph ratings were very small and not significant. The random errors ranged from 0.33 to 0.42. The interobserver agreement on photograph rating was moderately high as indicated by weighted kappa values between 0.57 and 0.76. The reliability coefficients were acceptable, ranging from 0.77 to 0.84 (Table 4.2). The differences in reproducibility parameters between the cast method and photographic method were small.

4.3.3 Comparison of casts with photographs

The intraobserver agreement between photograph and dental cast rating was high to very high, as indicated by weighted kappa coefficients of between 0.66 and 0.85 (Table 4.3). The reliability coefficients for the intraobserver agreement of the four observers ranged from 0.78 to 0.90, confirming the high intraobserver agreement. The random error varied from 0.25 to 0.37 GOSLON points.

The systematic differences between the cast and photograph method were small and not significant.

Table 4.3 *Intraobserver agreement between picture and dental cast ratings.**

Observer	Systematic differences	Random errors	Reliability	Weighted kappa
A-A	0.00	0.25	0.90	0.85
B-B	-0.04	0.35	0.80	0.69
C-C	0.00	0.29	0.88	0.81
D-D	0.02	0.37	0.78	0.66
Mean		0.32	0.84	0.75

* Systematic differences between cast and photograph method (GOSLON pt), random errors (GOSLON pt), reliability coefficients and weighted kappa values (n=49 patients). A, B, C, D = four different observers.

4.4 Discussion

4.4.1 Statistical method

There are two main ways in presenting quality parameters for a measurement instrument based on interobserver studies: quality characteristics for metric scales (i.e., systematic difference, random error, and reliability coefficient) as estimated by the Pearson correlation coefficient, and a quality characteristic for nominal scales (i.e., the kappa value). It is common practice to present kappa values as the quality parameter for the GOSLON Yardstick,[8,11,12] but this is not beyond discussion. The GOSLON Yardstick is an ordinal scale for which both the nominal (weighted kappa) and the metric (errors in GOSLON points) method may be applied.[13] The disadvantage of the nominal approach is that only kappa values can be calculated, which is known to be context dependent. In other words, kappa tells how well the measurement instrument performs in the context of the study under discussion. When the context changes (e.g., other subgroups or treatments), the kappa will also change. The random error (and often the systematic difference) does not change with its context of application. The aim of this reproducibility study was to provide the reader with general information about the photograph method as expressed by the random error and systematic difference, independent of its context. In the environment of systematic differences and random errors, reliability coefficients are more appropriate than kappa values, which are presented only for the sake of completeness.

4.4.2 General findings

The GOSLON Yardstick is widely used to assess treatment outcome based on dental arch relationships of patients with UCLP. In this study dental arch relationships were presented by five images of each set of dental casts, and these photographs were used for rating. The three views in occlusion were chosen to properly assess the anteroposterior relationship that is the most important aspect in the GOSLON classification. The occlusal views were presented to assist the rating of arch form.

The photographs of the reference models can be printed or put on an additional screen during photograph rating. In this study the observers printed off the reference patients; this enabled them to easily overview all the reference images of the different GOSLON groups at the same time. This facilitates a comparison between reference patients of adjacent categories and the patient to be judged, especially in borderline cases.

The results of this study showed a high intra- and interobserver agreement for the GOSLON classification on dental casts. This is in accordance with the results of Mars et al.[6,8] and Morris et al.,[12] who showed good inter- and intraobserver reliability for the GOSLON Yardstick when applied to dental casts only. The quality parameters for the GOSLON Yardstick applied to photographs were in the same range as for the dental casts scoring indicating that this medium is a reliable alternative to casts. Although the reliability of the photograph method proved to be good, during the rating sessions the observers sometimes experienced difficulties in assessing the overjet. During dental cast rating, the observers can easily judge the overjet by rotating the models. This is, of course, not possible in the photograph method in which only frontal, right, and left images of the dental casts in occlusion are available. The amount of overjet as well as the presence of incisal contact are important parameters for allocating a GOSLON score 1 to 3 because incorrect overjet assessment during photograph classification might shift the patient to another category, especially in borderline cases. This problem could be overcome when three-dimensional virtual dental casts become more widely used, enabling observers to rotate the dental casts in all directions on the screen.[14]

From this study it can be concluded that GOSLON rating with the use of photographs is a consistent, reproducible method for rating the dental arch relationships of patients with UCLP at the age of 9 years and is a reliable alternative to the application of the GOSLON Yardstick to dental casts. Future cleft audit or intercenter research studies could be conducted more efficiently following CD or e-mail transfer. For intercenter studies or remote clinical audit, the images could be placed on a password-protected Web site allowing other researchers or accredited raters anywhere in the world to undertake scoring. Together with training packages for new users, this method could increase the accessibility of proposed regional Good Practice Archives.[15]

Acknowledgments. The authors thank Ortholab BV (Doorn, The Netherlands) for their kind assistance in making the photographs of the dental casts. They also appreciate the help of Phil Eyres of the University of Manchester during the rating sessions.

4.5 References

1. Pruzansky S, Aduss H. Archform and the deciduous occlusion in complete unilateral clefts. *Cleft Palate J*. 1964;1:411-418.
2. Matthews D, Broomhead I, Grossmann W, Orth D, Goldin H. Early and late bone grafting in cases of cleft lip and palate. *Br J Plast Surg*. 1970;23:115-129.
3. Huddart AG, Bodenham RS. The evaluation of arch form and occlusion in unilateral cleft palate subjects. *Cleft Palate J*. 1972;9:194-209.
4. Crabb JJ, Foster TD. Growth defects in unrepaired unilateral cleft lip and palate. *Oral Surg Oral Med Oral Pathol*. 1977;44:329-335.
5. Björk A, Krebbs A, Solow B. A method for epidemiological registration of malocclusion. *Acta Odontol Scand*. 1964;22:27-41.
6. Mars M, Plint DA, Houston WJB, Bergland O, Semb G. The Goslon Yardstick: a new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate J*. 1987;24:314-322.
7. Hathorn I, Roberts-Harry D, Mars M. The Goslon Yardstick applied to a consecutive series of patients with unilateral clefts of the lip and palate. *Cleft Palate Craniofac J*. 1996;33:494-496.
8. Mars M, Asher-McDade C, Brattström V, Dahl E, McWilliam J, Mølsted K, Plint DA, Prahl-Andersen B, Semb G, Shaw WC, The RPS. A six-center international study of treatment outcome in patients with clefts of the lip and palate: part 3. Dental arch relationships. *Cleft Palate Craniofac J*. 1992; 29:405-408.
9. Dahlberg G. Statistical methods for medical and biological students. New York: Interscience Publications; 1940.
10. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1997;33:159-174.
11. Noverraz AEM, Kuijpers-Jagtman AM, Mars M, Van ’t Hof MA. Timing of hard palate closure and dental arch relationships in unilateral cleft lip and palate patients: a mixed longitudinal study. *Cleft Palate Craniofac J*. 1993;30:391-396.
12. Morris DO, Roberts-Harry D, Mars M. Dental arch relationships in Yorkshire children with unilateral cleft lip and palate. *Cleft Palate Craniofac J*. 2000;37:453-462.
13. Cohen ME. Analysis of ordinal dental data: evaluation of conflicting recommendations. *J Dent Res*. 2001;80:309-313.

14. Garino F, Garinon GB. Comparison of dental arch measurements between stone and digital casts. *World J Orthod*. 2002;3:250-254.
15. World Health Organization. Global strategies to reduce the health-care burden of craniofacial anomalies: report of WHO meetings on International Collaborative Research on Craniofacial Anomalies, Geneva, Switzerland, November 5-8, 2000. Park City, Utah; May 24-26, 2001.

Chapter 5

Nasolabial appearance in unilateral cleft lip and palate: A comparison with Eurocleft

Pieter JPM Nollet
Anne Marie Kuijpers-Jagtman
Athina Chatzigianni
Gunvor Semb
William C Shaw
Ewald M Bronkhorst
Christos Katsaros

Accepted by J Craniomaxillofac Surg, 2006

Summary

Objective: To evaluate nasolabial appearance of patients with UCLP treated in Nijmegen and to compare them with the six individual centers from the Eurocleft study. Relationships between ratings in nasolabial esthetics and dental arch relationships were also investigated.
Patients: Children with complete UCLP (n=42 consecutive cases) from the Nijmegen Cleft Palate Unit, the Netherlands.
Methods: Nasolabial appearance was assessed by applying an esthetic index and subsequently compared with the six-center Eurocleft study.
Results: The 90% central range for the overall esthetic rating of the 42 Nijmegen patients is 2.0 to 3.7 on a scale from 1 to 5 (1= very good nasolabial appearance, 5= very poor nasolabial appearance). With regard to the overall esthetic rating, Nijmegen showed similar treatment outcomes with Eurocleft centers A, D, E and F. Nijmegen scored significantly better than Eurocleft center C and significantly worse than Eurocleft center B ($p \leq 0.05$). No significant correlations between esthetic ratings and dental arch relationships could be established for the Nijmegen patients.
Conclusion: Comparisons of treatment protocol could not explain differences in treatment results. The current comparative study is supportive in the selection of patient records that are suitable for the "good practice archive" which is part of the EUROCRAN project.

5.1 Introduction

A major goal of cleft lip and palate treatment is to improve the esthetic appearance of the face and thus enhance the social acceptability of the individual in society.[1] It is widely accepted that facial appearance is important in forming first impressions and acts as a cue for social stereotyping.[2] By far the most common features to be the focus of teasing are appearance of the nose and the lip when compared with teasing about speech, appearance of teeth and facial appearance.[3] Improvements in the appearance of the lip and nose are the most frequently desired aspects for further treatment by patients with clefts and their parents.[3]

There is still no widely accepted standard rating method to assess facial esthetics in cleft lip and palate. Intercenter comparison is hampered by the reporting on facial esthetics with the use of different esthetic indices. A method that has become quite popular over the past decade, however, is an index developed by Asher-McDade et al.[4] This index was used in the Eurocleft study,[5] the CSAG study[6] and the Eurocleft follow-up study.[7] It was further employed, in modified form, in a Scandinavian intercenter study[8] and the index was the basis for the development of a standardized method of video recording the nasolabial area of patients with unilateral cleft lip and palate (UCLP).[9]

Other rating methods for nasolabial esthetics in cleft lip and palate were introduced by Tobiasen et al.,[10] Tobiasen and Hiebert,[11] and Johnson and Sandy.[12] The advantages of the use and acceptance of one standard rating method for facial esthetics in cleft lip and palate are obvious for comparisons between protocols, centers, and individuals. Individual esthetic scores could be of value in determining the necessity for secondary surgery. In addition, a standardized esthetic index could be helpful to inform patients about the expected treatment result after corrections of the nose or lip.

Despite the advantages of intercenter comparisons, there are also important limitations. Sample size, logistic problems and costs may be an issue. For most cleft teams, however, it is sufficient to know whether they are achieving results that are in line with other centers, nationally and internationally. Therefore, it was decided to set up a so-called "good practice archive" within the EUROCRAN project, the successor of the Eurocleft project, which started in 2000.[13] Such an archive should contain relevant clinical records that are considered to be representative of good practice. Other cleft centers could use these data to assess and compare their quality of care. The six centers in the Eurocleft study have already been rated and a wide diversity in treatment outcome was found.[13] Therefore, it was decided to investigate if data derived from the Nijmegen cleft lip and palate unit, where a large sample of consecutive cases with standardized records is available, could be added to the good practice archive. This required comparative studies with the Eurocleft sample for different components of treatment outcome. The first of a series of comparative studies between Nijmegen and Eurocleft showed that the Nijmegen patients could be compared with the best centers of the Eurocleft study with respect to dental arch relationships.[14] The aim of the present study was to evaluate the nasolabial appearance of Nijmegen patients with UCLP and to compare them with the six centers from the Eurocleft study. Furthermore, relationships between ratings in nasolabial esthetics and dental arch relationships were investigated.

5.2 Material and subjects

5.2.1 Subjects

Subjects for esthetic evaluation were 43 children (consecutive cases) with a complete unilateral cleft lip and palate, born in the years 1976-1986 and treated at the Nijmegen Cleft Palate Craniofacial Unit. Patients with Simonart's bands as well as patients with syndromes were excluded. All patients had to be registered at the Nijmegen Center within 3 months after birth and before any surgical intervention. All Nijmegen patients were operated by two surgeons. Frontal and profile photographs at age 9 (range 7.9 to 10.3 years) were selected for esthetic evaluation. One patient had to be excluded because there was no photographic material at this age available. So the final sample size was 42.

Table 5.1 *Treatment protocols of the centers A through F (Eurocleft) and Nijmegen (adapted from Shaw et al.[18])**

	A†	**B**	**C**	**D**	**E**	**F**	**Nijmegen**
Birth	**PSOT Hotz**			**PSOT extra-oral strapping**		**PSOT (T-traction)**	**PSOT (Hotz)**
2-6 mo	Lip closure (Millard, Skoog), 3-4 mo	Lip closure (Tennison) and vomer plasty, 2 mo	Lip closure (variation of methods + timing), within 6 mo	Lip closure (variation of methods + timing), within 6 mo	Lip closure (Millard) and vomer plasty, 3 mo	Lip closure (modified Skoog, Tennison-Randall) and bone grafting, 4-6 mo	Lip closure (Millard), 6-8 mo
9 mo	Soft palate closure (Von Langenbeck, Perko, Wardill, Kriens), 9-15 mo						
12 mo			Palate closure (various methods and timing), 12 mo	Palate closure (various methods and timing), within 2 yr		Palate closure (Veau-Wardill-Kilner), 12 mo	Soft palate closure (modified Von Langenbeck palatoplasty), 12-14 mo
18 mo					Palate closure (modified Von Langenbeck) 18-20 mo		
22 mo		Palate closure (Wardill Pushback), 22 mo					
9 yr	Bone grafting, hard palate closure	Bone grafting	Bone grafting	Bone grafting	Bone grafting	Bone grafting (only in cases with failure of primary bone graft)	Bone grafting and hard palate closure (Von Langenbeck), 9-11 yr (before 1985: variable timing of hard palate closure)

** PSOT: presurgical orthopedic treatment*

† It must be taken into consideration that center A did not adhere completely to this protocol. Only 31% of the patients received PSOT, in 31% of the patients also periosteoplasty was performed at lip closure and 23% of the patients had one-stage palatal closure around 13 months of age.[19]

In Nijmegen during the last 20 years the soft palate was closed at 12 to 14 months of age, while the hard palate was left open to be closed at the age of 9 to 11 years together with the bone grafting procedure for the alveolar cleft. The Nijmegen treatment protocol is described in Table 5.1. For patients that were born before 1985, the timing of hard palate closure was variable. For this study only patients with a two-stage palatal closure with closure of the hard palate after the age of 4 were included.

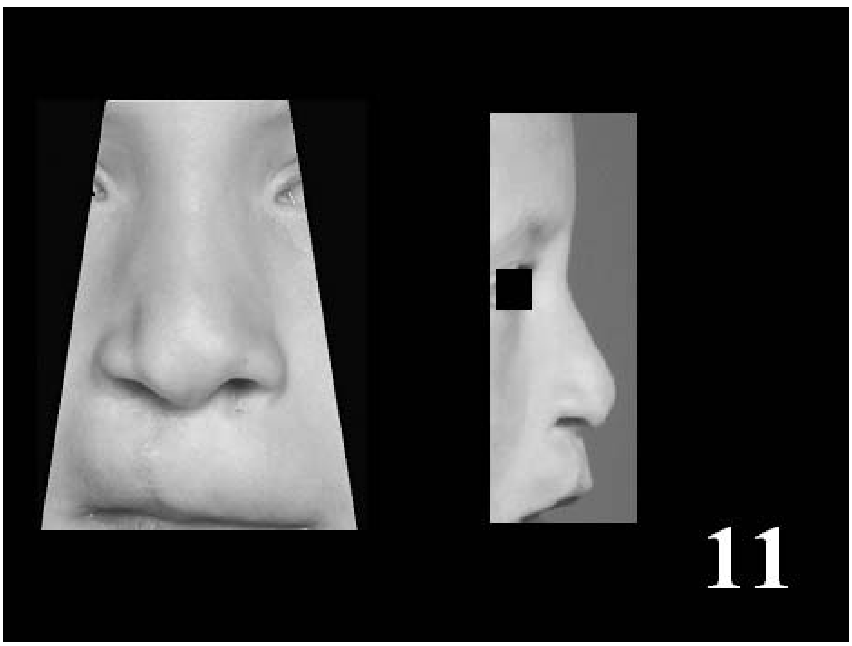


Figure 5.1 *Frontal and profile nasolabial view for unilateral cleft lip and palate patient with the identifying case number.*

5.2.2 Methods

The 42 Nijmegen patients were evaluated with an esthetic index developed by Asher-McDade et al.[4] In this index four nasolabial components (nasal form, nose symmetry, vermilion border, and nasal profile) are rated separately on five point scales where score 1 means a very good appearance, score 2 a good appearance, score 3 a fair appearance, score 4 a poor appearance and score 5 a very poor appearance. Asher-McDade et al.[4] found that judgement of the nasolabial area could be influenced by the surrounding facial features unrelated to the cleft itself, and therefore, like in the Eurocleft study,[5] the Nijmegen frontal and profile photographs were cropped to show only the nose and the lip. The frontal and profile nasolabial areas were loaded into PowerPoint, and each slide contained a profile and frontal view of one patient together with the identifying case number (Figure 5.1).

Replicate scorings were made on 14 randomly selected cases in order to assess intra-rater reliability. These 14 duplicated cases were randomly ordered between the 42 patients; thus a total of 56 sets of records were used for assessment. The 56 PowerPoint slides were scored by two Nijmegen raters (A.K., P.N.) and two Manchester raters (G.S., W.S.). The two Manchester raters have also been raters in the Eurocleft study where the esthetic rating index has been utilized.[5] A practice rating task was set so that the panel of raters could familiarize themselves with the scale prior to the experimental assessments.

Subsequently, the esthetic scores for the Nijmegen patients were compared with the esthetic outcome of the six individual centers from the Eurocleft study,[5] where the patients were also scored at the mean age of 9 years (range 8.0 to 10.9 years). The treatment protocols of these centers can be seen in Table 5.1.

Finally, possible relationships between the esthetic ratings of the Nijmegen patients and the dental arch relationships of the same patient group were investigated. The dental arch relationships of the 42 patients had been rated before in another study with the use of the GOSLON Yardstick.[14] The GOSLON Yardstick is a rating method specifically developed to grade dental arch relationships in the late mixed and/or early permanent dentition in children with UCLP.[15] The GOSLON classification method ranks patients with UCLP on a five-point scale where 1 indicates very good, 2 indicates good, 3 indicates fair, 4 indicates poor and a GOSLON score 5 indicates very poor dental arch relationships. The esthetic ratings for nasolabial components as well as the total esthetic rating were correlated with the GOSLON scores to study potential relationships.

5.2.3 Statistical analysis

To reduce variability and following Asher-McDade et al.,[4,5] the scores for the 4 observers were averaged for each individual nasolabial component as well as for the sum of the four sub scores. This is only allowed if there is sufficient coherence among the observers and, therefore, Cronbach's alpha was calculated for each individual nasolabial component as well as for the sum of the four sub scores. Both in describing the Nijmegen population and in the analysis of differences between centers, the mean scores over the four observers were used in the result section. Replicate measurement errors for the mean of the panel of judges were calculated to express the difference between the replicated scores (in esthetic points) and the intra-raters reliability was established with the use of Spearman's correlation coefficients.

To compare the six Eurocleft centers and Nijmegen non-parametric methods, e.g. Kruskal Wallis, would be the method of choice. However, this requires the availability of the scores of the individual patients evaluated in the various centers. These scores could not be made available, so only the information reported in literature, mean and standard deviation, could be used.[5] Therefore, t-tests were applied to compare treatment outcome as expressed by average esthetic scores for the individual nasolabial components as well as for the sum of its scores. The level of significance was set at $p \leq 0.05$.

Spearman's correlation coefficients were computed to investigate potential relationships between the esthetic (sub) ratings and the GOSLON scoring.

5.3 Results

5.3.1 Reliability of the method

The reliability for the four individual nasolabial ratings among the four observers was found to be good as indicated by Cronbach's alpha values ranging from 0.73 to 0.83 (Table 5.2). The reliability for the mean of the four sub scores (overall score) among the four observers was also found to be high (Table 5.2). These figures imply that the coherence among the four raters for the individual nasolabial ratings as well as for the mean of the four sub scores was satisfactory.

Table 5.2 *Coherence for the four naso labial sub scores and the overall score over the 42 Nijmegen patients, based on the individual scorings of the four raters.*

	Nasal deviation	Nasal form	Nasal profile	Vermilion border	Overall score
Cronbach's alpha	0.78	0.81	0.73	0.82	0.83

Both for the individual nasolabial subratings and for the sum of the four subratings, replicate measurement errors (n=14) for the mean of the four raters' scores were small and the intra-rater reliability for the mean of the four raters' scores was good (Table 5.3).

Table 5.3 *Replicate measurement errors (in esthetic points) and intra-rater reliability (Spearman's correlation coefficient) (n=14) for the four nasolabial sub scores as well as for the overall score, based on the mean scores of the four raters.*

	Nasal deviation	Nasal form	Nasal profile	Vermilion border	Overall score
Replicate measurement error	0.18	0.18	0.41	0.35	0.16
Spearman's correlation coefficient	0.87	0.93	0.56	0.94	0.96

5.3.2 Treatment outcome for nasolabial appearance

Figure 5.2 shows the esthetic distribution for the 42 Nijmegen patients per nasolabial component as well as for the overall esthetic scoring. The 90% central ranges for the nasal deviation, nasal form, nasal profile and vermilion border were 2.0 to 4.0, 2.0 to 4.5, 1.5 to 4.2 and 2.0 to 4.3, respectively. The 90% central range for the overall esthetic rating was 2.0 to 3.7.

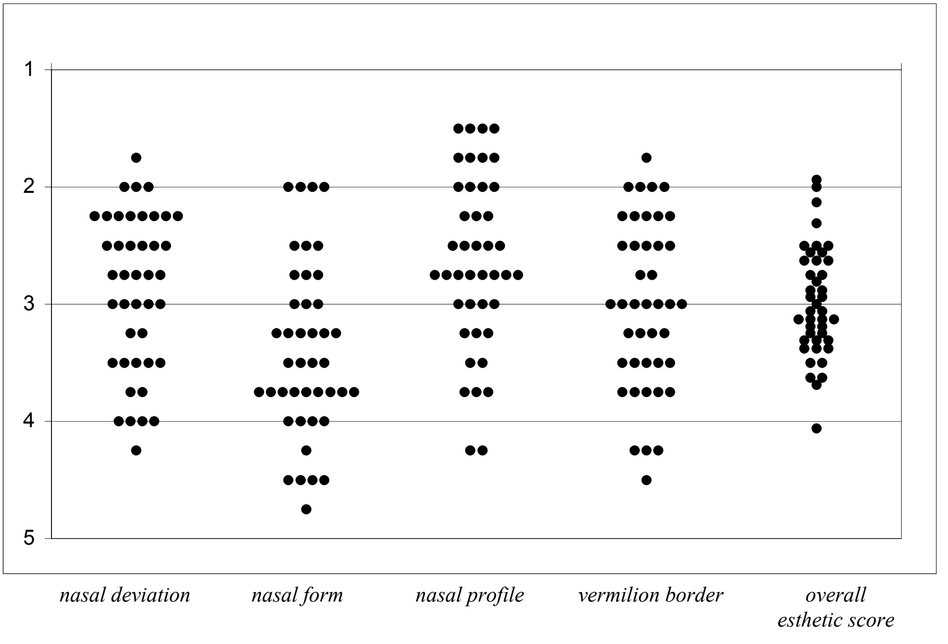


Figure 5.2 *The esthetic scores for the 42 Nijmegen patients depicted for the four nasolabial components as well as for the overall esthetic score. Each black dot represents the mean esthetic score over the 4 observers for one patient.*

Tables 5.4, 5.5, 5.6, 5.7 show the comparison between the Nijmegen center and the Eurocleft centers, using the means of the four raters' scores for the four individual nasolabial features.

Table 5.4 *Comparison of the six Eurocleft centers with the Nijmegen center (N) regarding the nasal deviation at 9 years of age.*

Center	Number	Mean esthetic score	SD	95% CI for the difference with Nijmegen (N) for nasal deviation	p-value
A	24	2.3	0.7	-0.94 to -0.26	0.00
B	27	2.7	0.9	-0.62 to 0.22	0.34
C	24	3.0	0.8	-0.29 to 0.49	0.61
D	25	2.5	0.9	-0.80 to 0.00	0.05
E	30	2.2	0.6	-1.00 to -0.40	0.00
F	19	2.8	0.6	-0.45 to 0.25	0.57
N	42	2.9	0.7		

For nasal deviation, Nijmegen showed no significant difference from Eurocleft centers B, C and F; Nijmegen achieved a relatively worse treatment outcome than center A, D and E. Regarding the nasal form, only center E showed significantly better results on the esthetic outcome than Nijmegen. With regard to the nasal profile, Nijmegen showed significantly better treatment outcome than centers A, C, D and E and with respect to the vermilion border Nijmegen scored significantly better than centers C and F.

Table 5.5 *Comparison of the six Eurocleft centers with the Nijmegen center (N) regarding the nasal form at 9 years of age.*

Centre	Number	Mean esthetic score	SD	95% CI for the difference with Nijmegen (N) for nasal deviation	p-value
A	24	3.2	0.7	-0.56 to 0.16	0.28
B	27	3.2	0.8	-0.58 to 0.18	0.30
C	24	3.6	0.6	-0.13 to 0.53	0.23
D	25	3.2	0.8	-0.59 to 0.19	0.31
E	30	3.0	0.8	-0.77 to -0.03	0.03
F	19	3.3	0.8	-0.53 to 0.33	0.64
N	42	3.4	0.7		

Table 5.6 *Comparison of the six Eurocleft centers with the Nijmegen center (N) regarding the nasal profile at 9 years of age.*

Center	Number	Mean esthetic score	SD	95% CI for the difference with Nijmegen (N) for nasal deviation	p-value
A	24	3.1	0.8	0.10 to 0.90	0.01
B	27	2.8	0.7	-0.15 to 0.55	0.26
C	24	3.5	0.6	0.57 to 1.24	0.00
D	25	3.2	0.5	0.30 to 0.90	0.00
E	30	3.2	0.7	0.26 to 0.94	0.00
F	19	2.8	0.8	-0.23 to 0.63	0.36
N	42	2.6	0.7		

Table 5.7 *Comparison of the six Eurocleft centers with the Nijmegen center (N) regarding the vermilion border at 9 years of age.*

Center	Number	Mean esthetic score	SD	95% CI for the difference with Nijmegen (N) for nasal deviation	p-value
A	24	3.0	0.6	-0.33 to 0.33	1.00
B	27	2.8	0.2	-0.44 to 0.04	0.09
C	24	3.3	0.5	-0.00 to 0.60	0.05
D	25	3.1	0.7	-0.26 to 0.46	0.58
E	30	3.0	0.8	-0.37 to 0.37	1.00
F	19	3.4	0.6	0.05 to 0.75	0.03
N	42	2.7	0.7		

Regarding the sum of the four nasolabial ratings, Nijmegen scored significantly better than Eurocleft center C and significantly less attractive than Eurocleft center B (Table 5.8).

Table 5.8 *Comparison of the six Eurocleft centers with the Nijmegen center (N) regarding the sum of the four nasolabial scores at 9 years of age.*

Center	Number	Mean esthetic score	SD	95% CI for the difference with Nijmegen (N) for nasal deviation	p-value
A	24	2.9	0.4	-0.32 to 0.12	0.36
B	27	2.8	0.3	-0.39 to -0.02	0.03
C	24	3.4	0.4	0.18 to 0.62	0.00
D	25	3.0	0.5	-0.25 to 0.25	1.00
E	30	2.8	0.6	-0.46 to 0.06	0.13
F	19	3.1	0.5	-0.17 to 0.37	0.46
N	42	3.0	0.5		

5.3.3 Nasolabial esthetics compared with dental arch relationships

Figure 5.3 presents the joint distribution of the GOSLON rating and the overall esthetic rating for the 42 Nijmegen patients. No significant correlation between the esthetic ratings and the GOSLON outcome could be established (Table 5.9).

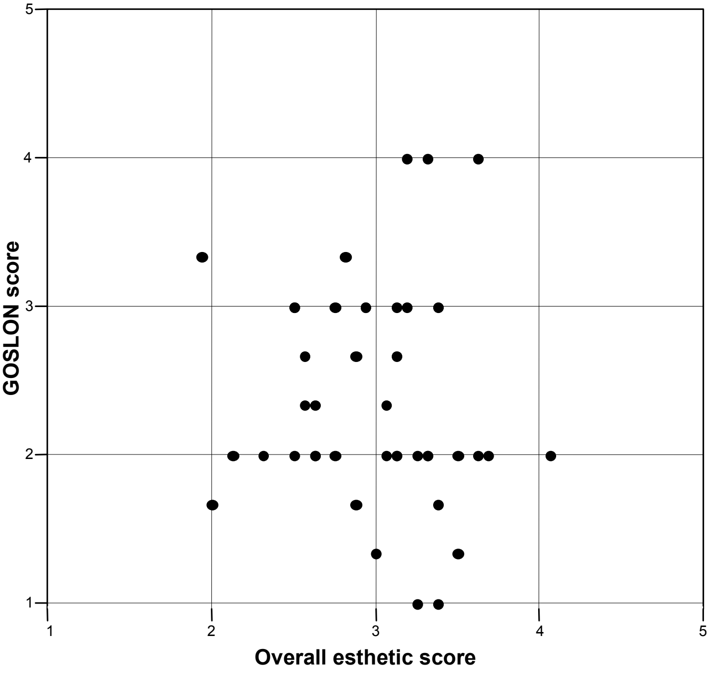


Figure 5.3 *Joint distribution of the GOSLON scores and the overall esthetic scores for the 42 Nijmegen patients at 9 years of age.*

Table 5.9 *Spearman's correlation coefficients of the esthetic ratings with the GOSLON rating for the Nijmegen patient group (n=42).*

	Spearman's correlation coefficient	**p-value**
Nasal deviation	-0.22	0.16
Nasal form	-0.28	0.08
Nasal profile	0.07	0.66
Vermilion border	0.08	0.61
Overall esthetic score	-0.16	0.33

5.4 Discussion

In this study nasolabial appearance was evaluated with the use of the esthetic rating method of Asher-McDade et al.[4] Like other studies where this rating method has been applied, the current study obtained good coherence among raters but relatively low inter-rater agreement. This might seem contradictory, but the good coherence indicates that raters agreed on the order of ranking of the patients whereas the relatively low inter-rater agreement indicates that the exact allocation of esthetic scores varied among raters. To reduce this variability, the observers' ratings were averaged, which is only allowed in case of sufficient coherence among raters. This resulted in a scoring method of reasonably high reproducibility and, like in earlier studies where the Asher-McDade rating method had been performed, an average score over the observers could reliably be used for nasolabial comparison between patient groups. However, since using this method implies that all patients need to be scored by more than just a few observers, this method is rather laborious.

Nijmegen and Eurocleft centers A, B and E had high volume operators but treatment protocols varied (Table 5.1). The extensive treatment protocol of Nijmegen included presurgical orthopedic treatment (PSOT) and a two-stage palatal closure, which do not give a significant benefit for the esthetic ratings when compared with Eurocleft centers B and E, where no PSOT was used and the anterior hard palate closure was performed simultaneously with lip closure at the age of 2 to 3 months by means of a vomer plasty (Table 5.1). Eurocleft centers C and D did not adhere to one strict treatment protocol but used a variety of methods and timing in lip as well as palatal closure. The relatively disappointing results of center C might have been due to the inconsistency of treatment protocol and/or the role of low volume surgeons. The treatment outcome of the current observational study showed that treatment protocol could not explain the differences in the esthetic ratings. This illustrates the need for a randomized clinical trial in which different elements of treatment protocols could be examined separately.

Prudence is in order when interpreting the differences in esthetic treatment outcome between centers. The inclusion criteria for the

Nijmegen patient group did not comprise patients with a Simonart's band whereas the Eurocleft study occasionally did include these patients. This could imply that the severity of the clefts at birth was larger in the Nijmegen patient group than for the Eurocleft groups, which could have influenced the ratings. Another limiting factor is that basic growth patterns of different populations are not always the same,[16] which could have had an impact on the nasal profile esthetic subrating as well.

Of all esthetic ratings, the nasal form subrating gives the poorest treatment scores in all six Eurocleft centers and also in Nijmegen. This indicates that regarding esthetics, nose form is obviously the key problem in unilateral cleft lip and palate. From this point of view, it would be very interesting to evaluate the treatment results of a patient group that underwent nasoalveolar molding (NAM).[17] However, so far NAM has not been studied in a randomized clinical trial design, so evidence based conclusions on the effect of NAM cannot be made at present.

The limitations of still photography are widely recognized, since it remains a two-dimensional representation with no analysis of function.[5,12] Standardized video recordings of the nasolabial area have been employed for appearance and function evaluation, but the reported agreement amongst plastic surgeons using this system was generally poor.[9] Despite the fact that direct subject evaluation may overcome the reported limitations of indirect media and provide the truest assessment of a subject, it has not been tested.[12]

Panel ratings of nasolabial appearance are not related to patients and parents' satisfaction with appearance.[6,3] This may be due to the lack of parents' opportunity to meet and compare results with other patients with clefts of a similar age. Another explanation is that parents perceive any surgery as an improvement over the initial cleft presentation.[6] Semb et al.[3] found in the six-center Eurocleft follow-up study that there are no associations between patient/parent dissatisfaction with nose and lip appearance and the corresponding amount of treatment. Neither was any relationship found between patient dissatisfaction and reported levels of teasing about the nose and lip. These findings illustrate that in order to understand the impact of treatment, nasolabial appearance should be judged also alongside other outcomes of cleft care including satisfaction with treatment, psychosocial adjustment and quality of life.

Individual correlations between esthetic scorings and GOSLON scoring for the dental arch relationships could not be established for the Nijmegen patients. Nor did the esthetic rankings between the six Eurocleft centers and Nijmegen follow the GOSLON ranking between the Eurocleft centers and Nijmegen.[14] This is surprising for the nasal profile subrating as the profile picture shows retardation of maxillary growth, an aspect which is incorporated in the main characteristics of the GOSLON rating: the anteroposterior dental arch relationships. The sometimes contradictory results for different components of treatment outcome show that cleft care should be evaluated for all its treatment components. In order to implement the good practice archive of the EUROCRAN project, clinical records for unilateral cleft lip and palate patients will be assembled including dental casts, photos, and cephalograms.[13] The current series of comparative studies between Nijmegen and the Eurocleft centers will be supportive to select those clinical records that are suitable for the good practice archive within the EUROCRAN project.

5.5 References

1. Marsh JL. Comprehensive care for craniofacial anomalies. *Curr Probl Pediatr*. 1980;10:1-43.
2. Tobiasen JM. Social judgements of facial deformity. *Cleft Palate Craniofac J*. 1987;24:323-327.
3. Semb G, Brattström V, Mølsted K, Prahl-Andersen B, Zuurbier P, Rumsey N, Shaw WC. The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 4: Relationship between treatment outcome, patient/parents satisfaction and the burden of care. *Cleft Palate Craniofac J*. 2005a;42:83-92.
4. Asher-McDade C, Roberts C, Shaw WC, Gallager C. Development of a method for rating nasolabial appearance in patients with clefts of the lip and palate. *Cleft Palate Craniofac J*. 1991;28:385-391.
5. Asher-McDade C, Brattström V, Dahl E, McWilliam J, Mølsted K, Plint DA, Prahl-Andersen B, Semb G, Shaw WC, The RPS. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 4.

Assessment of nasolabial appearance. *Cleft Palate Craniofac J*. 1992;29:409-412.

6. Williams AC, Bearn D, Mildinhall S, Murphy T, Sell D, Shaw WC, Murray JJ, Sandy JR. Cleft lip and palate care in the United Kingdom - The clinical standards advisory group (CSAG) study. Part 2: Dentofacial outcomes and patient satisfaction. *Cleft Palate Craniofac J*. 2001;38:24-29.
7. Brattström V, Mølsted K, Prahl-Andersen B, Semb G, Shaw WC: The Eurocleft study. Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 2: Craniofacial form and nasolabial appearance. *Cleft Palate Craniofac J.* 2005;42:69-77.
8. Brattström V, McWilliam J, Larson O, Semb G. Craniofacial development in children with unilateral clefts of the lip, alveolus, and palate treated according to three different regimes. *Scand J Plast Reconstr Hand Surg.* 1992;26:313-319.
9. Morrant DG, Shaw WC. Use of standardized video recordings to assess cleft surgery outcome. *Cleft Palate J*. 1996;33:134-142.
10. Tobiasen JM, Hiebert JM, Boraz RA. Development of scales of severity of facial cleft impairment. *Cleft Palate Craniofac J*. 1991;28:419-424.
11. Tobiasen JM, Hiebert JM. Facial impairment scales for clefts. *Plast Reconstr Surg*. 1994;93:31-41.
12. Johnson N, Sandy J. An aesthetic index for evaluation of cleft repair. *Eur J Orthod.* 2003;25:243-249.
13. Shaw WC, Semb G. Eurocleft - An experiment in intercenter collaboration. In: Berkowitz, S: Cleft lip and palate. Berlin Heidelberg: Springer; 2006:765-776.
14. Nollet PJPM, Katsaros C, Van 't Hof MA, Semb G, Shaw WC, Kuijpers-Jagtman AM. Treatment outcome after two-stage palatal closure in unilateral cleft lip and palate: A comparison with Eurocleft. *Cleft Palate Craniofac J*. 2005;42:512-516.
15. Mars M, Plint DA, Houston WJB, Bergland O, Semb G. The Goslon Yardstick: A new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate J.* 1987;24:314-322.
16. Trenouth MJ, Davies PHJ, Johnson JS. A statistical comparison of three sets of normative data from which to derive standards for craniofacial measurement. *Eur J Orthod*. 1985;7:193-200.
17. Grayson BH, Maull D. Nasoalveolar molding for infants born with clefts of the lip, alveolus and palate. In: Berkowitz, S: Cleft lip and palate. Berlin Heidelberg: Springer; 2006:451-458.

18. Shaw WC, Asher-McDade C, Brattström V, Dahl E, McWilliam J, Mølsted K, Plint DA, Prahl-Andersen B, Semb G, The RPS. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 1. Principles and study design. *Cleft Palate Craniofac J*. 1992;29:393-397.
19. Semb G, Brattström V, Mølsted K, Prahl-Andersen B, Shaw WC. The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 1: Introduction and treatment experience. *Cleft Palate Craniofac J*. 2005b;42:64-68.

Chapter 6

Long-term cephalometric evaluation of craniofacial development in unilateral cleft lip and palate after delayed hard palatal closure

Pieter JPM Nollet
Christos Katsaros
Rinske WF Huyskens
Wilfred A Borstlap
Ewald M Bronkhorst
Anne Marie Kuijpers-Jagtman

Submitted for publication

Summary

This long-term cephalometric study aimed to evaluate craniofacial development of patients with a complete UCLP treated with a two-stage palate closure, including delayed closure of the hard palate. Prediction models for cephalometric outcome at age 18 were developed with the help of cephalometric values at the ages 9 and 12 years. Moreover, the objective need for surgery at age 18 was predicted from cephalometric values at age 9. Cephalograms of 43 consecutive patients with a complete UCLP from the Nijmegen Cleft Unit were analyzed at 9, 12 and 18 years. The patient group showed a retrusive craniofacial growth pattern for the maxilla and mandible, and a rather vertical growth pattern for the lower face. Using multiple linear regression, for most cephalometric variables, 40 to 80% of the cephalometric values at early adulthood could be explained by cephalometric values at the ages 9, 12, and gender or by the cephalometric values at age 9 only, and gender. Several cephalometric variables at age 9 (s-n-ss, s-n-pg, sss-ns-sms, sss-ns-pgs) were found significant predictors for the need for surgery at age 18. The need for surgery at age 18 was correctly predicted from age 9 for 85% of the investigated patient group.

6.1 Introduction

Longitudinal evaluation of treatment outcome provides a valuable source of data for the general study of craniofacial growth and development in unilateral cleft lip and palate (UCLP) and for comparison of patterns of development of unoperated clefts, non-cleft controls or cleft groups with different treatment protocols. Previous cephalometric studies of unoperated individuals with UCLP and comparable non-cleft controls have found deviations of craniofacial morphology.[1,2] Besides group characteristics, mean cephalometric values represent a useful basis for evaluating the progress of individual patients and for identifying individuals with particular growth disturbances that may call for a modified approach to treatment.[3] Furthermore, these data could be useful in creating a model in which one can predict treatment outcome at adult age from treatment results at a younger age. This would be particularly helpful for early adversely developing patients upon whom orthognathic surgery at a latter age could be expected.

Traditionally, of all interventions during cleft lip and palate treatment, palatal repair has been considered to have the greatest influence on subsequent craniofacial growth and development.[4] However, for many years, there has been much controversy about the timing of palatal closure. Some investigators advocated early hard palatal closure,[3,5] whereas others suggested that delayed hard palate closure would result in more favorable growth of the maxilla.[6,7,8] Unfortunately, long-term longitudinal studies on this subject are relatively rare and the controversy on the optimal timing of palatal closure illustrates the need for longitudinal evaluations of craniofacial growth and development in UCLP.[9,10]

The aim of this long-term study was to evaluate craniofacial growth and development of patients with a complete UCLP treated with a two-stage palate closure, including delayed closure of the hard palate, and to develop prediction models for cephalometric outcome at adulthood. Moreover, it was attempted to relate the objective need for surgery at early adulthood to the craniofacial morphology at age 9.

6.2 Material and methods

6.2.1 Subjects

Cephalograms of 43 consecutively treated Caucasian patients with a complete UCLP and treated at the Nijmegen Cleft Palate Center were included for longitudinal evaluation. Patients with Simonart's bands and patients with syndromes were excluded. All patients (27 boys, 16 girls) were born between 1976 and 1986 and had to be registered at the Nijmegen Cleft Palate Craniofacial Center within 3 months after birth and before any surgical intervention. The surgical and orthodontic treatment protocol is described in Table 6.1. In Nijmegen, during the past 20 years, the soft palate was closed at 12 to 14 months of age, whereas the hard palate was left open to be closed at the age of 9 to 11 years together with the bone grafting procedure. For patients born before 1985, timing of hard palatal closure was variable. For this cephalometric study, only patients with closure of the hard palate after the age of 4 were included.

Table 6.1 *Treatment protocol for the Nijmegen unilateral cleft lip and palate patients born between 1976-1986.*

Age	Procedure
Birth	PSOT (Hotz)
6-8 mo	Lip closure (Millard)
12-14 mo	Soft palate closure (modified Von Langenbeck palatoplasty)
9-11 yrs	Hard palate closure together with bone grafting procedure (Boyne and Sands[25]) (Before 1985: variable timing of hard palate closure)
12-15 yrs	Conventional orthodontic treatment with fixed appliances Fixed retention upper jaw
15-19 yrs	Lip / nose correction
19-21 yrs	Pre- and postsurgical orthodontics with fixed appliances Orthognatic surgery
	Prosthetic replacement of teeth

6.2.2 Methods

Lateral cephalograms were obtained in centric occlusion with the patient positioned in an Evald cephalostat and oriented to the Frankfort horizontal plane. The mean age at which the cephalograms were taken was 8.5 years (SD=0.5), 12.0 years (SD=1.2) and 17.9 years (SD=1.2). Because of loss of follow-up of a few patients, 42 cephalograms were available at age 12, and 40 cephalograms were available at age 18 for cephalometric evaluation. Three patients (one boy, two girls) underwent an osteotomy between the second and third cephalogram, and the postoperative cephalograms of these 3 patients were not included for longitudinal cephalometric evaluation at age 18 as this would create an overestimation of good treatment outcome at this age. All cephalograms were scanned on a 12 bit scanner (R2 ImageChecker M5000 DM, R2 Technology, Inc., Sunnyvale, USA) and digitized according to the Eurocleft protocol[11] by one observer (PN) who was calibrated by the principal investigator of the cephalometric part of the Eurocleft study. Digitization of the cephalograms was performed with Viewbox® (dHal Orthodontic Software, Athens, Greece), a software program for cephalometric analysis. Figure 6.1 illustrates the digitized points and reference lines used in the study. The cephalometric analysis consisted of 14 angular and 2 ratio variables and was based on the Eurocleft study.[11] To assess the measurement error, cephalograms of 20 randomly selected patients at the three different ages were digitized twice by the same investigator (PN) with a time interval of 2 months. Thus, 60 cephalograms were used for the intra-observer assessment.

In order to predict the need for surgery at age 18 from the cephalometric craniofacial morphology at the ages 9 and 12, the patients at age 18 were divided into two groups (need for surgery at age 18 yes/no). A negative overjet at age 18 was considered an indication for a combined orthodontic-surgical approach, and a positive overjet was considered to represent no need for orthognathic surgery. In end-to-end situations, the need for surgery was assessed by the position of the skeletal bases together with the inclination of the upper and lower incisors. The patients of the last age group were judged for their need of surgery by two investigators (PN and CK); 8 patients were found to have

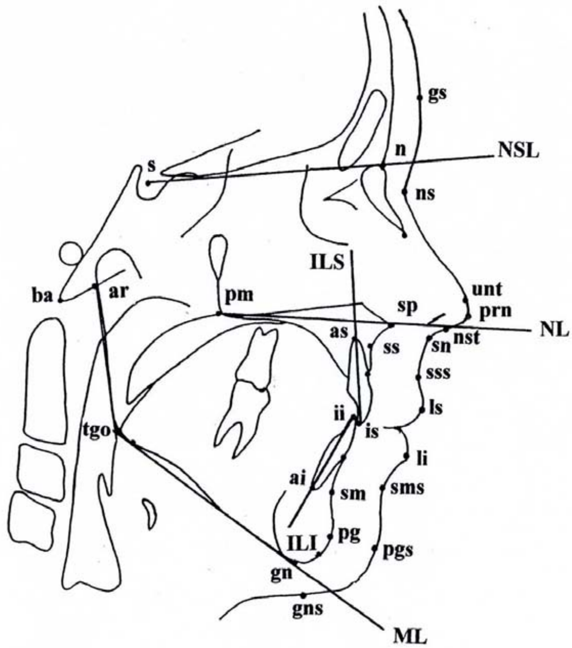


Figure 6.1 *Reference points on the profile cephalometric radiographs.*

Skeletal reference points: ***ai*** *= Apex inferius. The apex of the root of the most prominent lower central incisor;* ***ar*** *= Articulare. The point at the intersection between the contours of the mandibular ramus and the occipital bone;* ***as*** *= Apex superius. The apex of the root of the most prominent upper central incisors;* ***ba*** *= Basion. The most posterior-inferior point on the clivus bone;* ***gn*** *= Gnathion. The most inferior point on the mandibular symphysis;* ***Ii*** *= Incision inferius. The incisal edge of the lower most prominent incisor;* ***is*** *= Incision superius. The incisal edge of the most prominent upper incisor;* ***n*** *= Nasion. The most anterior point of the frontonasal suture;* ***pg*** *= Pogonion. The most anterior point on the mandibular symphysis;* ***pm*** *= Pterygo-maxillare. The intersection of the nasal floor and the posterior contour of the maxilla;* ***s*** *= Sella. The center of the sella turcica;* ***sm*** *= Supramentale (B-point). The deepest point on the anterior contour of the lower anterior process;* ***sp*** *= Spina nasalis anterior. The apex of the anterior nasal spine;* ***ss*** *= Subspinale (A-point). The deepest point on the anterior contour of the upper alveolar arch;* ***tgo*** *= Gonion tangent point. The point of intersection between the mandibular line and the ramus line.*
Soft tissue reference points: ***gs*** *= Soft tissue glabella. The most anterior point on the soft tissue glabella;* ***gns*** *= Soft tissue gnathion. The soft tissue point overlying gn;* ***li*** *= Labrale inferius. The most prominent point on the prolabium of the upper lip;* ***ls*** *= Labrale superius. The most prominent point on the prolabium of the upper lip;* ***ns*** *= Soft tissue nasion. The deepest point on the frontonasal curvature;* ***nst*** *= Nasal septum tangent point. The anterior tangent point to the tangent to the nasal septum through sn;* ***pgs*** *= Soft tissue pogonion. The most prominent point on the chin;* ***prn*** *= Pronasale. The most prominent point on the apex of the nose;* ***sms*** *= Soft tissue supramentale. The point of the greatest concavity in the midline of the lower lip;* ***sn*** *= Subnasale. The deepest point in the nasolabial curvature;* ***sss*** *= Soft tissue subspinale. The point of greatest concavity or convexity in the midline of the upper lip;* ***unt*** *= Upper nasal tangent point from ns.*
Skeletal reference lines: ***ILI*** *= axis of lower incisors. A line from ii to ai;* ***ILS*** *= axis of upper incisors. A line from is to as; ML = Mandibular line. The tangent to the lower border of the mandible through gn;* ***NL*** *= Nasal line. The line through sp and pm;* ***NSL*** *= Nasion-sella-line. The line through n and s. (Reprinted with permission of Brattström et al., 2005[11]).*

a need for a surgical-orthodontic approach and 29 patients had no indication for surgery. Three patients already underwent an osteotomy before the age 18. So, 11 out of 40 patients (27.5%) were included in the need for surgery group at age 18. The objective need for surgery (yes/no) at age 18 was related to the cephalometric outcome at the ages 9 and 12.

6.2.3 Statistical analysis

Duplicate measurement errors for the cephalometric digitizations were calculated according to Dahlberg's[12] formula, and reliability coefficients between first and second digitization were calculated as Pearson correlation coefficients. The presence of systematic differences between first and second digitization was investigated using paired t-tests.

Means and SDs of the cephalometric variables at the different ages are presented. Increments between cephalometric values at the different ages were analyzed using paired t-tests.

Multiple linear regression was used in order to explain the cephalometric values at the age 18 using the values at the ages 9 and 12. A second multiple linear regression model was used in order to explain the cephalometric values at the age of 18 using the cephalometric values at the age 9 only. For both regression analyses, gender was added as an independent variable to investigate the difference in cephalometric increments between sexes. As the cephalograms were not taken at exactly the same age within each age group, the age at which the cephalogram was made was taken as a co-variable to obtain unbiased estimates of the effects of the independent variables for both regression models.

Backward logistic regression was applied to assess the effects of the cephalometric morphology at age 9 on the decision to operate at age 18. Because of the small number of patients in the surgery group, the number of variables needs to be limited. Therefore, the most relevant cephalometric variables (s-n-ss, ss-n-sm, s-n-pg, n-sp/n-gn *100, sss-ns-sms, sss-ns-pgs) were selected. In the backward logistic regression procedure, the threshold for removal was set at p=0.10.

6.3 Results

In Table 6.2, for all cephalometric variables the results of the paired t-tests between the first and second digitization, the reliability coefficients between first and second digitization and the duplicate measurement errors are presented. For two cephalometric variables (gs-prn-pgs and NSL/ML), a statistically significant difference between the first and second digitization was found. The reliability coefficients of all variables ranged from 0.958 to 0.997; duplicate measurement errors of angular variables ranged from 0.26º to 0.97º.

Table 6.2 *Intra-observer assessment between first and second digitization (n=60). Systematic differences with p-values are the results of paired t-tests. The reliability coefficients were calculated as Pearson correlation coefficients and duplicate measurement errors were calculated by Dahlberg's[12] formula.*

Cephalometric variable	Differences between digitations	p-values	Reliability coefficients	Duplicate measurement errors
Hard tissue variables				
s-n-ss (°)	-0.06	0.28	0.995	0.32
ss-n-sm (°)	-0.01	0.87	0.996	0.28
s-n-pg (°)	0.09	0.23	0.992	0.41
NSL/NL (°)	0.30	0.01	0.981	0.59
NSL/ML (°)	-0.01	0.93	0.993	0.48
n-sp/n-gn *100 (ratio)	-0.02	0.86	0.958	0.47
Ils/NL (°)	-0.07	0.69	0.992	0.93
Ils/Ili (°)	0.07	0.70	0.995	0.97
Soft tissue variables				
sss-ns-sms (°)	0.00	0.97	0.995	0.26
sss-ns-pgs (°)	-0.01	0.85	0.993	0.33
gs-prn-pgs (°)	-0.44	0.00	0.993	0.68
gs-sn-pgs (°)	0.04	0.82	0.990	0.82
ns-unt/NSL (°)	0.09	0.40	0.986	0.60
ns-prn-sn (°)	-0.12	0.23	0.992	0.52
nst-sn-ls (°)	-0.24	0.07	0.997	0.74
ns-sn/ns-gns *100 (ratio)	-0.01	0.95	0.958	0.44

In Table 6.3, descriptive statistics (means and SDs) of the 16 cephalometric variables (14 angular and 2 ratio measurements) at the different ages are presented. Both the maxilla and mandible showed a retrusive facial pattern. For both the skeletal and the soft tissue values a rather vertical growth pattern was found for all ages. The interincisal angle (Ils/Ili) was obtuse, especially at age 9. The nasolabial angle (nst-sn-ls) was rather obtuse for the ages 9 and 12 and the angulation of the nose in the sagittal plane (ns-prn-sn) was found to be rather favorable, especially at the ages 9 and 12.

Table 6.3 *Mean cephalometric values with SD at age 9, 12 and 18 years.*

Cephalometric variable	**Age 9 (n=42)**		**Age 12 (n=42)**		**Age 18 (n=37)**	
	Mean	SD	Mean	SD	Mean	SD
Hard tissue variables						
s-n-ss (°)	77.5	3.7	75.5	4.2	74.3	4.5
ss-n-sm (°)	4.6	2.5	2.2	3.3	-0.4	3.8
s-n-pg (°)	73.4	3.9	73.8	4.2	75.7	4.7
NSL/NL (°)	10.4	3.4	10.0	3.9	9.5	3.6
NSL/ML (°)	37.4	6.1	37.8	6.7	35.7	6.9
n-sp/n-gn*100	44.2	2.0	44.5	2.3	44.1	2.0
Ils/NL (°)	95.9	7.8	100.5	9.1	111.0	6.3
Ils/Ili (°)	147.4	10.3	142.9	12.1	131.7	12.1
Soft tissue variables						
sss-ns-sms (°)	7.2	2.7	5.2	3.1	3.3	3.6
sss-ns-pgs (°)	5.8	3.0	3.8	3.7	1.4	4.2
gs-prn-pgs (°)	150.7	5.6	148.5	6.4	146.4	7.9
gs-sn-pgs (°)	189.4	6.3	187.6	7.4	183.9	9.2
ns-unt/NSL (°)	103.8	4.6	104.5	5.0	106.7	4.7
ns-prn-sn (°)	109.6	4.4	107.0	5.6	101.8	5.7
nst-sn-ls (°)	107.2	11.2	107.4	11.0	100.0	10.0
ns-sn/ns-gns *100	41.3	2.8	42.2	2.8	42.4	2.3

In Table 6.4, for all variables the increments of the cephalometric values between the three different age periods are presented. Both the skeletal and soft tissue values for the maxilla indicated an ongoing retrusion during ageing. The retrognatic mandible showed an increase for the sagittal skeletal values and a retrusion for the sagittal soft tissue values during ageing. The vertical growth pattern did not change so much between the different ages, although the vertical soft tissue increments indicated a slight increase during ageing. The interincisal angle became less obtuse at a latter age, which is also reflected by an increasing angle between upper incisor and palatal plane during ageing. Both the angulation of the nose (ns-prn-sn) and the nasolabial angle (nst-sn-ls) decreased between 12 and 18 years of age. Figure 6.2 gives a visual impression of the mean craniofacial development from age 9 to 18 for the Nijmegen patient group.

Table 6.4 *Increments of cephalometric values between 9 and 12, and 12 and 18 years of age.*

Cephalometric variable	Increments cephalometric values between 9 and 12 years of age (n=42)			Increments cephalometric values between 12 and 18 years of age (n=37)		
	Mean	SD	p	Mean	SD	p
Hard tissue variables						
s-n-ss (°)	-2.0	2.3	0.00	-1.4	2.8	0.03
ss-n-sm (°)	-2.4	2.2	0.00	-2.6	2.5	0.00
s-n-pg (°)	0.5	2.0	0.11	1.9	2.5	0.00
NSL/NL (°)	-0.4	3.3	0.44	-0.7	3.8	0.53
NSL/ML (°)	0.2	2.4	0.64	-2.1	3.4	0.00
n-sp/n-gn*100	0.3	2.0	0.35	-0.3	1.6	0.37
Ils/NL (°)	4.8	9.5	0.00	9.7	9.0	0.00
Ils/Ili (°)	-4.5	9.6	0.00	-10.0	11.8	0.00
Soft tissue variables						
sss-ns-sms (°)	-1.9	1.8	0.00	-1.8	1.9	0.00
sss-ns-pgs (°)	-2.1	2.1	0.00	-2.4	2.2	0.00
gs-prn-pgs (°)	-2.1	3.7	0.00	-2.5	3.9	0.00
gs-sn-pgs (°)	-1.8	3.6	0.00	-3.5	5.1	0.00
ns-unt/NSL (°)	0.6	2.8	0.15	2.1	3.0	0.00
ns-prn-sn (°)	-2.6	4.3	0.00	-5.2	5.3	0.00
nst-sn-ls (°)	0.2	9.2	0.91	-6.6	10.2	0.00
ns-sn/ns-gns *100	1.0	1.6	0.00	0.5	2.0	0.24

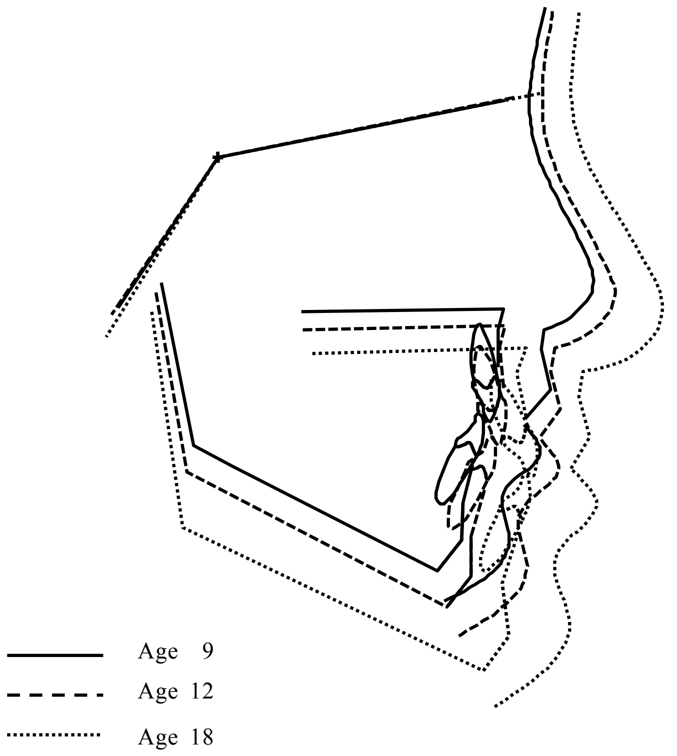


Figure 6.2 *Mean tracings illustrating the craniofacial morphology in UCLP at age 9 (black lines, n=43), age 12 (red lines, n=42) and age 18 (blue lines, n=37). Tracings are superimposed along the sella-nasion line and registered at sella (S).*

In Tables 6.5 and 6.6, the results of the linear regression analyses aiming at the prediction of the cephalometric values for age 18 are given. In both regression models, the percentages explained variance varied widely, although for most of the cephalometric values at age 18, 40 to 80% of the variance could be explained by the cephalometric values at a younger age. In both regression models, gender did not play a significant role in predicting the values of the oldest age group, given the presence of the other independent variables/cephalometric values of the younger age group(s). For every cephalometric variable, a prediction model can be extracted from Tables 6.5 and 6.6. For example, if one wants to predict “s-n-ss” at age 18, using the “s-n-ss” angles at age 9 and 12, gender (m/f) and exact age of the cephalograms at around age 9 and 12, the value at age 18 can be predicted by using the following equation: “s-n-ss$_{18}$” ≙ 5.77 + 0.13 “s-n-ss$_9$” + 0.75 “s-n-ss$_{12}$” + 1.15 gender - 1.52 (“actual age ceph 9 years” - 9) - 0.05 (“actual age ceph 12 years” - 12).

Table 6.5 *Multiple regression model for the 16 dependent variables at age 18 and the independent variables (cephalometric variables at age 9, gender (m/f)). The cells with a light gray background indicate a a variable not reaching statistical significance (p>0.05). Beta gives the effect of the increase of 1 unit of the independent variable on the dependent variable.*

Cephalometric variable at age 18	Adj R2 (% expl var)	Const	Cephalometric variable at age 9		Gender (m=0/f=1)		Age correction at 9 years
			p	beta (95%-CI)	p	beta (95%-CI)	beta
s-n-ss (°)	0.493	6.69	0.000	0.85 (0.57;1.14)	0.612	0.57 (-1.68;2.81)	-1.86
ss-n-sm (°)	0.368	-6.19	0.000	0.98 (0.57;1.39)	0.246	1.26 (-0.91;3.43)	-0.86
s-n-pg (°)	0.533	6.89	0.000	0.94 (0.64;1.23)	0.549	-0.70 (-3 .03;1.64)	-1.09
NSL/NL (°)	0.275	3.68	0.001	0.56 (0.25;0.87)	0.577	0.59 (-1.55;2.74)	1.36
NSL/ML (°)	0.668	-1.28	0.000	0.98 (0.74;1.22)	0.483	0.99 (-1.84;3.82)	0.98
n-sp/ n-gn *100	0.438	16.24	0.000	0.63 (0.37;0.89)	0.416	-0.42 (-1.46;0.62)	-0.06
Ils/NL (°)	0.014	89.86	0.153	0.21 (-0.08;0.51)	0.410	-1.79 (-6.15;2.57)	-3.48
Ils/Ili (°)	0.033	85.8	0.156	0.32 (-0.13;0.76)	0.233	5.00 (-3.39;13.38)	3.20
sss-ns-sms (°)	0.655	-4.13	0.000	1.16 (0.88;1.45)	0.880	-1.11 (-1.62;1.39)	0.86
sss-ns-pgs (°)	0.598	-4.31	0.000	1.11 (0.78;1.43)	0.570	-0.55 (-2.50;1.40)	0.69
gs-prn-pgs (°)	0.568	-14.76	0.000	1.07 (0.73;1.40)	0.837	0.40 (-3.50;4.29)	-0.53
gs-sn-pgs (°)	0.586	-18.52	0.000	1.14 (0.80;1.48)	0.893	-0.30 (-4.77;4.18)	-0.40
ns-unt/NSL (°)	0.540	34.49	0.000	0.71 (0.48;0.94)	0.886	-0.16 (-2.38;2.07)	1.22
ns-prn-sn (°)	0.341	30.80	0.001	0.68 (0.32;1.05)	0.944	0.12 (-3.31;3.55)	1.18
nst-sn-ls (°)	0.239	46.96	0.001	0.50 0.23;0.77	0.977	0.09 (-6.15;6.33)	0.33
ns-sn/ ns-gns *100	0.550	17.85	0.000	0.59 (0.39;0.78)	0.374	-0.49 (-1.59;0.61)	-0.98

Table 6.6 *Multiple regression model for the 16 dependent variables at age 18 and the independent variables (cephalometric variables at age 9, cephalometric variables at age 12, gender (m/f)). The cells with a light gray background indicate a variable not reaching statistical significance (p>0.05). Beta gives the effect of the increase of 1 unit of the independent variable on the dependent variable.*

Ceph. variable at age 18	**Adj R2 (% expl var)**	**Const**	**Cephalometric variable at age 9**		**Cephalometric variable at age 12**		**Gender (m=0/f=1)**		**Age correction at 9 years**	**Age correction at 12 years**
			p	beta (95%-CI)	p	beta (95%-CI)	p	beta (95%-CI)	beta	beta
s-n-ss (º)	0.647	5.77	0.567	0.13 (-0.34;0.60)	0.001	0.75 (0.34-1.16)	0.280	1.15 (-0.98;3.27)	-1.52	-0.05
ss-n-sm (º)	0.606	-3.93	0.572	0.14 (-0.37;0.65)	0.000	0.85 (0.47;1.23)	0.066	1.87 (-0.14;3.87)	-0.68	0.33
s-n-pg (º)	0.732	1.94	0.762	-0.07 (-0.57;0.42)	0.000	1.07 (0.61;1.52)	0.359	-0.93 (-2.96;1.10)	-1.26	-0.32
NSL/NL (º)	0.372	3.04	0.034	0.38 (0.03;0.73)	0.051	0.30 (-0.00;0.59)	0.964	-0.05 (-2.29;2.19)	1.64	0.66
NSL/ML (º)	0.785	2.51	0.500	-0.19 (-0.75;0.38)	0.000	1.09 (0.61;1.57)	0.290	1.31 -1.17;3.78	1.94	0.58
n-sp/ n-gn *100	0.706	13.59	0.045	0.23 (0.01;0.46	0.000	0.46 (0.27;0.65)	0.015	-1.03 (-1.85;-0.22)	-0.01	0.26
Ils/NL (º)	0.206	70.94	0.864	0.03 (-0.28;0.33)	0.007	0.37 (0.11;0.63)	0.141	-3.29 (-7.73;1.15)	-3.13	-0.43
Ils/Ili (º)	0.303	60.19	0.367	-0.22 (-0.70;0.27)	0.001	0.74 (0.33;1.15)	0.366	3.69 (-4.53;11.91)	3.77	1.62
sss-ns-sms (º)	0.744	-3.01	0.070	0.45 (-0.04;0.94)	0.001	0.68 (0.29;1.06)	0.683	0.31 (-1.22;1.84)	0.58	0.27
sss-ns-pgs (º)	0.757	- 2.79	0.450	0.19 (-0.32;0.70)	0.000	0.88 (0.48;1.29)	0.765	0.27 (-1.54;2.06)	0.47	0.55
gs-prn-pgs (º)	0.753	-25.42	0.197	0.27 (-0.15;0.69)	0.000	0.87 (0.50;1.24)	0.701	0.65 (-2.77;4.07)	-1.68	0.07
gs-sn-pgs (º)	0.688	-19.95	0.279	0.31 (-0.27;0.89)	0.002	0.83 (0.32;1.33)	0.570	-1.32 (-6.40;3.39)	-1.02	-0.66
ns-unt/NSL (º)	0.668	29.59	0.809	0.05 (-0.38;0.48)	0.001	0.70 (0.29;1.11)	0.294	-1.13 (-3.30;1.04)	1.79	0.13
ns-prn-sn (º)	0.336	22.23	0.067	0.45 (-0.03;0.94)	0.067	0.35 (-0.03;0.73)	0.519	-1.19 (-4.92;2.54)	1.59	0.36
nst-sn-ls (º)	0.305	39.26	0.066	0.31 (-0.02;0.65)	0.142	0.27 (-0.94;0.63)	0.812	-0.85 (-8.05;6.36)	0.97	1.69
ns-sn/ ns-gns*100	0.601	13.61	0.178	0.22 (-0.11;0.55)	0.014	0.46 (0.10;0.82)	0.086	-1.04 (-2.24;0.16)	-0.900	-0.86

In Table 6.7, the resulting logistic backward regression model is presented. It can be interpreted that within the investigated patient group for every increase of 1º of the s-n-ss angle at age 9, the odds for a combined orthodontic-surgical approach at age 18 decreases with 44.8%.

Table 6.7 *Remaining variables from backward logistic regression analysis for the indication to operate at age 18. The regression analysis was applied with selected cephalometric variables (s-n-ss, ss-n-sm, s-n-pg, n-sp/n-gn *100, sss-ns-sms, sss-ns-pgs) at age 9.*

Remaining variables at age 9		
	p-value	**exp (beta) (95%-CI)**
s-n-ss (º)	0.023	0.552 (0.331; 0.922)
s-n-pg (º)	0.061	1.615 (0.979; 2.664)
sss-ns-sms (º)	0.019	0.385 (0.173; 0.857)
sss-ns-pgs (º)	0.033	2.406 (1.074; 5.390)

Table 6.8 shows the proportions of predicted and actual need for surgery at the age of 18 for the investigated patient group. It can be seen that for 64% of the patients that were found to have an objective need for surgery at age 18, surgery could correctly be predicted from age 9; for 93% of the patients that were found to have no need for surgery at age 18, no surgery was predicted at age 9. The need for surgery (yes/no) at age 18 has been correctly predicted at age 9 for 85% of the investigated patient group.

Table 6.8 *Predicted need and actual need for a combined orthodontic-surgical approach at age 18 for the Nijmegen patient group. Predicted need is calculated with the help of logistic backward regression and selected cephalometric variables at age 9.*

n=40	**Predicted need for surgery from age 9**			
Actual need for surgery at age 18		No operation	Operation	% correctly predicted need for surgery (y/n)
	No operation	27	2	93%
	Operation	4	7	64%
				85%

6.4 Discussion

In this study, evaluation of craniofacial growth and development has been based on cephalometric outcome. In our cephalometric analysis, for two out of sixteen cephalometric variables, a systematic difference between first and second digitization was found. However, for all cephalometric variables, the duplicate measurement error was small in comparison with the standard deviations of the measurements and the standard deviations of the cephalometric increments. In addition, to minimize the method error, cephalometric values were obtained from digitization sessions where the three cephalograms of one patient were digitized in chronological order, starting with the cephalogram at the youngest age. By contrast, the intra-observer assessment was based on comparisons of cephalometric values of the same cephalograms digitized with a time interval of 2 months. Therefore, it can be assumed that the actual intra-observer error is smaller than presented in Table 6.2.

Characteristic findings in the soft tissue profile in children with UCLP are a short upper lip[13] and flattening of the nose.[14] In the present study, flattening of the nose (ns-unt/NSL) was not found, although the nasolabial angle (nst-sn-ls) increased considerably during ageing. However, caution should be exercised in the interpretation and comparison of cephalometric soft tissue values. Cephalometric analyses of the soft tissue do not include the asymmetry seen in frontal view of children with UCLP. In addition, soft tissue cephalometric evaluation depends on the co-operation of the patient since it is essential that the patients keep their lips in a relaxed position while the lateral radiograph is being taken.[15]

When interpreting the present cephalometric outcome, it should be considered that increments of cephalometric values are a combined result of craniofacial growth and development as well as treatment. All palate repair procedures have the potential for some inhibitory effect in all dimensions[9] and the decrease of maxillary prominence (s-n-ss) during ageing in the present delayed hard palate closure group seems to follow a comparable pattern. Other published longitudinal evaluations in UCLP also show a decrease of maxillary prominence during ageing, both for

UCLP patients with early and delayed hard palatal closure.[3,6,16,17] The observed craniofacial growth pattern in the present UCLP group is in line with the cephalometric studies of Smahel et al.[18] and Hermann et al.[19,20] where bimaxillary retrognathia, shortening of the mandible, and a vertical growth pattern of the lower face was found for UCLP patients. Hermann et al.[19,20] found these craniofacial growth patterns in babies at 2 months of age before any operation was performed, which supports the hypothesis of a special craniofacial type in unilateral cleft lip and palate individuals.

Unfortunately, present literature does not provide conclusive evidence about the optimal timing of hard palate repair on craniofacial growth in patients with cleft lip and palate. Liao and Mars[10] showed in a systematic review that several studies concluded that variation in the timing of hard palate repair does not affect the protrusion of the maxilla (s-n-ss) significantly, while others opposed this view. This illustrates that there is reason to opt for a randomized controlled clinical trial (RCT) in early versus delayed hard palate closure. In such RCT, craniofacial growth and development should be assessed, along with other parameters of treatment outcome like speech, psychosocial aspects, and burden of care. At the moment, the question “early versus late hard palatal closure" is incorporated in the ongoing Scandcleft project, a RCT among 10 Scandinavian and British centers to elucidate the best timing and technique of primary surgery in unilateral cleft lip and palate, which is part of the EUROCRAN project.[21]

It is difficult to reliably interpret the differences in cephalometric treatment outcome among centers. Firstly, there is no uniform approach for the set-up of cephalometric studies: cephalometric reference points and reference planes, cephalometric variables, statistical analyses and the ages at which cephalograms are taken differ among studies. Secondly, basic growth patterns of different populations are not always the same. For example, in a cephalometric comparison of different groups of non-cleft children, Trenouth et al.[22] showed that Dutch children are relatively more skeletal Class II when compared with British children. Finally, it is difficult to ascribe a more favorable cephalometric outcome to the relating intervention or factor. For example, is it the type of surgery, the skills of the surgeon, the age at which the operation was performed or a genetic component, which is responsible for a good or less favorable treatment result?

In the present paper, it was attempted to explain cephalometric outcome at age 18 by gender and cephalometric outcome at the ages 9 and 12. Therefore, linear regression analyses were applied and, for most of the cephalometric variables at age 18 in both linear regression models, 40 to 80% of the variance could be explained by the independent variables. In a recently published study on the prediction of facial growth in UCLP,[23] the sagittal jaw relationships at 15 years of age could be predicted with an accuracy of up to 1 degree in 60 to 75% of the patients. As still considerable amount of growth takes place after the age of 15 years, this prediction has limited clinical value. In our model, the poorest explained variance was found for those cephalometric variables that included the incisors (Ils/NL and Ils/Ili). The low explained variance for these variables could have been expected since the inclination of the incisors generally changes significantly between 9 and 18 years of age as a result of orthodontic treatment. The relatively low explained variance of the nasolabial angle (nst-sn-ls) might be caused by a slightly different lip posture on the cephalograms at the different ages for some of the investigated patients.

In the present linear regression models, gender did not play a significant role in explaining cephalometric outcome at a latter age. This conclusion is in line with Krogman et al.[24] and Semb[3] where no sex difference for angular and/or ratio measurements could be established during longitudinal cephalometric evaluation of unilateral cleft lip and palate patients. However, for linear cephalometric measurements, both Krogman et al.[24] and Semb[3] found significant differences between boys and girls, but these measurements were not included in the current regression models.

In linear regression models, the percentage explained variance is a reliable indicator of model performance. For logistic regression, however, such an indicator does not exist. Here, the percentage of correctly predicted patients does give information on the model performance. But this percentage is sensitive for the fact that the population used to construct the model is the same as the one used to evaluate the model performance. This results in a positively biased estimate of the predictive power of the logistic model. Therefore, to test the true power of the prediction model, it would be useful to apply the current logistic regression analysis on another comparative cleft group.

In conclusion, this long-term study of treatment outcome in UCLP patients treated with a two-stage palatal closure, including delayed hard palatal closure, generally shows a retrusive growth pattern for the maxilla and mandible, and a rather vertical growth pattern for the lower face. Most of the present cephalometric variables at age 18 could, to a certain extent, be explained from cephalometric values at the ages 9 and 12. Moreover, the need for surgery at adulthood was correctly predicted from age 9 for 85% of the investigated patient group. Application of the current logistic regression analysis on another comparative cleft group would assess the true power of the prediction model.

Acknowledgements. The authors would like to thank Kirsten Mølsted, associate professor and head of the Cleft Palate Department, Copenhagen, Denmark, for the calibration sessions.

6.5 References

1. Capelozza Filho L, Taniguchi SM, Silva Filho OG. Craniofacial development of adult unoperated complete unilateral cleft lip and palate patients. *Cleft Palate Craniofac J*. 1993;30:376-381.
2. Mars M, Houston WJB. A preliminary study of facial growth and morphology in unoperated male unilateral cleft lip and palate subjects over 13 years of age. *Cleft Palate J*. 1990;27:7-10.
3. Semb G. A study of facial growth in patients with unilateral cleft lip and palate treated by the Oslo CLP team. *Cleft Palate Craniofac J*. 1991;28:1-21.
4. Friede H, Katsaros C. Current knowledge in cleft lip and palate treatment from an orthodontist's point of view. *J Orofac Orthop*. 1998;59:313-330.
5. Huddart AG. A comparative study of treatment and occlusion in unilateral cleft palate subjects. *Trans Eur Orthod Soc*. 1972:167-176.
6. Friede H, Enemark H. Long-term evidence for favorable midfacial growth after delayed hard palate repair in UCLP patients. *Cleft Palate J*. 2001;38:323-329.

7. Hotz MM, Gnoinski WM. Effects of early maxillary orthopaedics in coordination with delayed surgery for cleft lip and palate. *J Maxillofac Surg 1979;*7:201-210.
8. Nollet PJPM, Katsaros C, van ’t Hof MA, Kuijpers-Jagtman AM. Treatment outcome in unilateral cleft lip and palate evaluated with the Goslon Yardstick: A meta-analysis of 1236 patients. *Plast Reconstr Surg*. 2005;116:1255-1262.
9. Kuijpers-Jagtman AM, Long RE. The influence of surgery and orthopedic treatment on maxillofacial growth and maxillary arch development in patients treated for orofacial clefts. *Cleft Palate Craniofac J*. 2000;37:527/1-12.
10. Liao YF, Mars M. Hard palate repair timing and facial growth in cleft lip and palate: A systematic review. *Cleft Palate Craniofac J.* published online 2005.
11. Brattström V, Mølsted K, Prahl-Andersen B, Semb G, Shaw WC. The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 2: Craniofacial form and nasolabial appearance. *Cleft Palate Craniofac J*. 2005;42:69-77.
12. Dahlberg G. Statistical methods for medical and biological students. New York: Interscience Publications; 1940.
13. Smahel Z, Müllerova Z. Craniofacial morphology in unilateral cleft lip and palate prior to palatoplasty. *Cleft Palate J.* 1986;23:225-232.
14. Sadowsky C, Aduss H, Pruzanksy S. The soft tissue profile in unilateral clefts. *Angle Orthod*. 1973;43:233-246.
15. Mølsted K, Asher-McDade C, Brattström V, Dahl E, Mars M, McWilliam J, Plint DA, Prahl-Andersen B, Semb G, Shaw WC, The RSP. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 2. Craniofacial form and soft tissue profile. *Cleft Palate Craniofac J*. 1992;29:398-404.
16. Brattström V, McWilliam J, Larson O, Semb G. Craniofacial development in children with unilateral clefts of the lip, alveolus, and palate treated according to four different regimes. 1. Maxillary development. *Scand J Plast Reconstr Surg Hand Surg*. 1991;25:259-267.
17. Paulin G, Thilander B. Dentofacial relations in young adults with unilateral complete cleft lip and palate. A follow-up study. *Scand J Plast Reconstr Surg Hand Surg*. 1991;25:63-72.
18. Smahel Z, Betincova L, Müllerova Z, Skvarilova B. Facial growth and development in unilateral complete cleft lip and palate from palate surgery up to adulthood. *J Craniofac Genet Dev Biol*. 1993;13:57-71.

19. Hermann NV, Jensen BL, Dahl E, Bolund S, Darvann TA, Kreiborg S. Craniofacial growth in subjects with unilateral complete cleft lip and palate, and unilateral incomplete cleft lip, from 2 to 22 months of age. *J Craniofac Genet Dev Biol*. 1999;19:135-147.
20. Hermann NV, Jensen BL, Dahl E, Bolund S, Kreiborg S. A comparison of the craniofacial morphology in 2-month-old unoperated infants with unilateral complete cleft lip and palate, and unilateral incomplete cleft lip. *J Craniofac Genet Dev Biol*. 1999;19:80-93.
21. Semb G. Multicenter trials in cleft lip and palate surgery. Presented at the International Collaboration on Craniofacial Anomalies, World Health Organization, Geneva, Switzerland, March 5-8, 2000.
22. Trenouth MJ, Davies PHJ, Johnson JS. A statistical comparison of three sets of normative data from which to derive standards for craniofacial measurement. *Eur J Orthod*. 1985;7:193-200.
23. Veleminska J, Smahel Z, Mullerova Z. Predicting the developments of jaws in patients with complete unilateral cleft of the lip and palate. *Acta Chir Plast*. 2005;47:81-84.
24. Krogman WM, Jain RB, Long, RE. Sex differences in craniofacial growth from one month to ten years in cleft lip and palate. *Cleft Palate J*. 1982;19:62-71.
25. Boyne PJ, Sands NR. Secondary bone grafting of residual alveolar and palatal clefts. *J Oral Surg*. 1972;30:87-92.

Chapter 7

General discussion

7.1 Introduction

Throughout the present thesis, treatment outcome after 2-stage palatal closure, including delayed closure of the hard palate, has been evaluated. The Nijmegen treatment results were compared in an international setting using the Eurocleft data. Treatment outcome with respect to dental arch relationships and facial esthetics of the Nijmegen patients with 2-stage palatal closure was comparable with the results of the Eurocleft centers with the best outcome (Chapter 2 and 5). However, treatment protocol (among which the palatal closure procedure) could not explain differences in the quality of treatment results. In a meta-analysis of the existing literature, it was shown that delayed hard palate repair resulted in better dental arch relationships than early hard palate closure, which allowed explanation of differences in treatment results by the timing of hard palate closure (Chapter 3). Longitudinal evaluation after delayed hard palate closure showed a craniofacial growth pattern with bimaxillary retrognathia, shortening of the mandible, and a vertical growth pattern of the lower face (Chapter 6). It was shown that dental arch relationships in UCLP could be reliably rated on the Internet using photographs of dental casts (Chapter 4), which will facilitate future evaluation and comparison of treatment outcome in cleft care.

In this chapter, the general results of the present thesis will be related and discussed. Some suggestions for future research are given.

7.2. Evaluation of treatment outcome

7.2.1 General remarks

Throughout the current study, it was encountered that reliable comparison and evaluation of published treatment outcome in UCLP was hindered by the absence of a uniform approach in cleft research. Firstly, there are still no widely accepted standard rating methods to assess treatment outcome in UCLP. Intercenter comparisons are hampered by the use of different esthetic indices, and the absence of one uniform cephalometric method with standardized cephalometric reference points and reference lines.

Moreover, the way of presenting treatment outcome in literature is rather inconsistent and complicates reliable comparisons of different patient groups. For example, the outcome of rating sessions with indices like the GOSLON Yardstick[1] and the esthetic index of Asher-McDade et al.[2] is sometimes presented as means and SDs, whereas sometimes the distribution of the scores is reported. Finally, the investigated (elements of) treatment protocols, as well as the examined patient group(s) are often inadequately described.

7.2.2 Treatment outcome

In most chapters of the present thesis, treatment outcome has been compared and evaluated at the age of 9 years. It would be of clinical value to know if the observed outcome at age 9 could be representative for treatment outcome at a later age. The results in the Eurocleft follow-up study reveal a pattern of consistency in the relationships between centers at age 9, 12 and 17 with regard to dental arch relationships, cephalometric outcome, and nasolabial appearance.[3,4] This might indicate that the observed significant differences between Nijmegen and the Eurocleft centers found at age 9 (Chapter 2 and 5) could also be found at a later age. The consistency in quality of treatment outcome during ageing in the Eurocleft follow-up study was confirmed by the long-term cephalometric evaluation of our own patients, where a consistent relationship from 9 to 18 years of age for most cephalometric variables was found (Chapter 6). However, further work on the long-term predictability from early outcome assessment is necessary, and longitudinal archives from cleft clinics from around the world could make a significant contribution to this work.

In the present thesis, conventional records (dental casts, photographs, and cephalograms) have been used for the evaluation and comparison of treatment outcome. The limitations of photography and cephalograms are well recognized, since they remain two-dimensional representations with no analysis of function. However, cephalograms, dental casts and photographs still form a part of the patient’s routine records, and are available in the archives of many cleft centers, which make these conventional records valuable for retrospective evaluation. At the time the photos and cephalograms were taken for the present study, three-dimensional low doses techniques like cone beam CT (CBCT) scanning were not yet available. In future studies, CBCT techniques will realize the incorporation of the third dimension, and they will provide excellent opportunities for imaging hard tissues structures in relation to most soft tissue components.[5]

It should be considered that for proper evaluation and comparison of treatment results in cleft lip and palate, treatment outcome should be evaluated along with other parameters of cleft care, like speech, hearing, and psychological aspects, which were not evaluated in the current thesis. The fact that treatment outcome for different components of treatment was sometimes contradictory (Chapter 5) confirms that conclusions based on evaluation of only one component of treatment outcome could be deceptive and are sometimes not representative for the standards of the delivered cleft care as a whole. This was confirmed in the Eurocleft follow-up study where no association between treatment outcome, treatment intensity and patient/parent satisfaction was found.[6] Thus, as the amount of treatment does not always correlate with the quality of clinical outcome, there is reason to emphasize on a treatment protocol that is the most cost-effective with a minimized burden for the patient, rather than adhering to demanding protocols that have no proven excess value.

7.3 Delayed hard palate repair

An essential part of the Nijmegen protocol for patients with UCLP is the concept of two-staged palate repair. The rationale for this treatment protocol is based on both theoretical considerations of maxillofacial growth and clinical results as shown by the Zürich group in the seventies of the last century.[7] Later on, experimental evidence from studies in dogs by Wijdeveld et al.,[8] In de Braekt et al.[9] and Leenstra et al.[10] provided experimental evidence that postponing palate surgery resulted in better dento-alveolar development and more favorable maxillary arch dimensions. This supports the concept of two-staged palate repair, including delayed closure of the hard palate, which has been employed in Nijmegen now for about 30 years.

In the mean time, in literature the controversy between early versus late hard palatal closure continued to be a topic of debate, which is well illustrated in a recent systematic review on hard palate repair timing and facial growth in cleft lip and palate.[11] Not only the effect of the palatal closure procedure on maxillofacial growth is main point of debate, but also the assumed negative effect on speech. It is argued that if the hard palate is left open till a later age, prolonged hypernasality, compensatory articulations, and a relatively high prevalence of retracted oral articulation would be the result.[12,13] A compromised speech would also have an impact on the psychosocial well-being of the youngster with an orofacial cleft.

Unfortunately, no standardized longitudinal speech records were available of the investigated Nijmegen patients with UCLP. Therefore, we focused on the aspect of maxillofacial development, also because there are hardly any long-term studies on evaluation of treatment outcome after delayed hard palate closure available from literature. Data on delayed hard palate closure, which are comparable to the data from the Nijmegen delayed hard palate closure group, come from Gothenburg in Sweden, where 2-stage palate closure has been performed since 1979. The Gothenburg patient group has been compared with an early hard palate closure group from Aarhus in Denmark, and it has been shown from a cephalometric comparison between 30 patients in both groups that delayed hard palatal closure had significantly better midfacial development,[14] which is in line with the results of the present meta-analysis (Chapter 3). However, the observed differences were small and the delayed hard palate group still showed a retrognathic facial pattern. Long-term speech comparison of the same two groups of patients showed that the speech obtained after delayed hard palate closure was as good as that achieved after conventional surgical habilitation. However, in some delayed hard palate closure patients, speech development did not normalize until the cleft in the hard palate had been closed.[15] Therefore, in 1994 the Gothenburg protocol changed so that the age at which hard palate closure was performed moved from 8 to 3 years of age.[16] Esthetic results on nasolabial appearance are not available from the Gothenburg delayed hard palate group.

In contrast with Friede and Enemark,[14] Noverraz et al.[17] found for a group of Nijmegen patients no difference in dental arch relationships between groups of patients with UCLP with hard palate repair at 1.5, 4.6, or 9.4 years of age. These findings could be explained from the study of Owman-Moll et al.[18] where it was shown that the cleft width of UCLP patients showed a marked reduction immediately after velar repair, but then, on average, remained stable until final surgical closure of the hard palate. Rohrich et al.[19] found neither growth differences in a long-term evaluation of adult patients with clefts having had palate repairs by the same surgeon at either 10 months or 4 years of age. However, they did find significantly greater speech deficiencies and occurrence of fistulas in the delayed palate repair group. This finding raises another important issue in this controversy, namely the additional burdens of treatment imposed by delayed palate surgery. With the possibility of prolonged speech therapy before the repair, the growth improvements could equally well be negated in value because of these other concerns. Concerns regarding speech and additional burdens of care might justify a 2-stage palatal repair with an earlier closure of the hard palate than the age of 9 years, which is the current age at which hard palate closure is performed for the Nijmegen cleft group. However, prospective, well-designed controlled studies, especially on long-term results, are urgently needed to take an evidence-based decision on timing of hard palate repair. At the moment, this question is incorporated in the ongoing EUROCRAN Scandcleft project, a randomized controlled clinical trial (RCT) of primary cleft lip and palate surgery among 10 Scandinavian and British centers to elucidate the best timing and technique of primary surgery in unilateral cleft lip and palate.[20] Results of future RCTs like Scandcleft will serve as a valuable indication into which direction the present Nijmegen treatment protocol should proceed.

7.4 Future directions in the evaluation of treatment outcome in UCLP

On the basis of the problems described above, recommendations for future evaluation of treatment outcome in UCLP could be made.

In order to facilitate easy comparison and evaluation among both individual cleft patients and cleft centers, standard-rating methods should be developed and widely used. To facilitate extensive use of standardized rating methods, identical record collection should be applied in every cleft center. The Eurocleft project 1996-2000 yielded consensus recommendations for timing and nature of record taking, including record taking methodology for photographs, dental casts and speech.[21] At a more recent meeting held under the auspices of the World Health Organization,[22] a global consensus on recommendations for record keeping was agreed. This defines minimum record keeping across a range of cleft types and treatment episodes for centers that might wish to participate in future international comparisons.[23] In the Good Archive Practice of the EUROCRAN project, records include dental casts, facial photos, and cephalograms, and standardization of record collection will be helpful for cleft teams to easily monitor the quality of their care. At the moment, three-dimensional record collection is progressing, and standardization of three-dimensional software as well as constancy and uniformity in its use is required to reliably compare treatment results of different cleft teams.

Another important recommendation for future research is that identical research designs and standard methodology should be used where possible. National and international collaborations should preferably be performed in a randomized controlled clinical trial (RCT), although it is clear that this is not always possible. For these instances, the set-up of prospective registries could be a good alternative to RCTs for evaluation and comparison of cleft care. Basic assumption is that the preferred identical research design should be feasible for many cleft centers. In addition to identical research designs and standard methodology, also the reporting on the patient group(s) examined and the description of the investigated methods and/or treatment options should be relevant, complete, and, where possible, internationally standardized.

7.5 References

1. Mars M, Plint DA, Houston WJB, Bergland O, Semb G. The Goslon Yardstick: a new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate J*. 1987;24:314-322.
2. Asher-McDade C, Roberts C, Shaw WC, Gallager C: Development of a method for rating nasolabial appearance in patients with clefts of the lip and palate. *Cleft Palate Craniofac J*. 1991;28:385-391.
3. Mølsted K, Brattström V, Prahl-Andersen B, Shaw WC, Semb G. The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 3: Dental arch relationships. *Cleft Palate Craniofac J*. 2005;42:78-82.
4. Brattström V, Mølsted K, Prahl-Andersen B, Semb G, Shaw WC: The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 2: Craniofacial form and nasolabial appearance. *Cleft Palate Craniofac J*. 2005;42:69-77.
5. Kau CH, Richmond S, Palomo JM, Hans MG. Current products and practice. Three-dimensional cone beam computerized tomography in orthodontics. *J Orthod*. 2005;32:282-293.
6. Semb G, Brattström V, Mølsted K, Prahl-Andersen B, Zuurbier P, Rumsey N, Shaw WC: The Eurocleft study: Intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 4: Relationship between treatment outcome, patient/parents satisfaction and the burden of care. *Cleft Palate Craniofac J*. 2005;42:83-92.
7. Hotz M, Gnoinki W. Effects of early maxillary orthopedics in coordination with delayed surgery for cleft lip and palate. *J Maxillofac Surg*. 1979;7:201-210.
8. Wijdeveld MGMM, Grupping EM, Kuijpers-Jagtman AM, Maltha JC. Maxillary arch dimensions after palatal surgery at different ages on Beagle dogs. *J Dent Res*. 1989;68:1105-1109.
9. In de Braekt MMH. Dento-alveolar development after modified palatal surgery on dogs. Ph.D. thesis. University of Nijmegen, Maastricht: Cortjens; 1992.
10. Leenstra TS, Maltha JC, Kuijpers-Jagtman AM, Spauwen PH. Wound healing in beagle dogs after palatal repair without denudation of bone. *Cleft Palate Craniofac J*. 1995;32:363-369.
11. Liao YF, Mars M. Hard palate repair timing and facial growth in cleft lip and palate: A systematic review. *Cleft Palate Craniofac J*. published online, 2005.

12. Lohmander-Agerskov A, Friede H, Lilja J et al. Delayed closure of the hard palate: a comparison of speech in children with open and functionally closed residual clefts. *Scand J Plast Reconstr Surg Hand Surg*. 1996;30:121-127.
13. Lohmander-Agerskov A. Speech outcome after cleft palate surgery with the Gothenburg regimen including delayed hard palate closure. *Scand J Plast Reconstr Surg Hand Surg*. 1998;32:63-80.
14. Friede H, Enemark H. Long-term evidence for favorable midfacial growth after delayed hard palate repair in UCLP patients. *Cleft Palate J*. 2001;38:323-329.
15. Lohmander-Agerskov A, Willadsen E. A comparison of long-term speech results following the delayed hard palate closure concept and a conventional two-stage vomer flap/push back procedure in UCLP patients. Presented at the sixth European Craniofacial Congress, Manchester, England, June 1999.
16. Lilja J, Mars M, Elander A, Enocson L, Hagsberg C, Worrell E, Batra P, Friede H. Analysis of dental arch relationships in Swedisch UCLP subjects: 20 year longitudinal consecutive series treated with delayed hard palate closure. *Cleft Palate Craniofac J*. published online, 2005.
17. Noverraz AEM, Kuijpers-Jagtman AM, Mars M, Van't Hof MA. Timing of hard palate closure and dental arch relationships in unilateral cleft lip and palate patients: a mixed longitudinal study. *Cleft Palate Craniofac J*. 1993;30:391-396.
18. Owman-Moll P, Katsaros C, Friede H. Development of the residual cleft in the hard palate after velar repair in a two-stage palatal repair regimen. *J Orofac Orthop*. 1998;59:286-300.
19. Rohrich RJ, Roswell AR, Johns DF, Drury MA, Grieg G, Watson DJ, Godfrey AM, Poole MD. Timing of hard palate closure: a critical long-term analysis. *Plast Reconstr Surg*. 1996;98:236-246.
20. Semb, G. Multicenter trials in cleft lip and palate surgery. Presented at the International Collaboration on Craniofacial Anomalies, World Health Organization, Geneva, Switzerland, March 5-8, 2000.
21. Shaw WC, Semb G, Nelson P, Brattström V, Mølsted K, Prahl-Andersen B, Gundlach KK. The Eurocleft Project 1996-2000: overview. *J Cranio-Maxillofac Surg*. 2001;29:131-140.
22. World Health Organization. Global strategies towards reducing the health-care burden of craniofacial anomalies. Report of WHO meetings on international collaborative research on craniofacial anomalies, WHO Human Genetics Programme, 2002.

23. Shaw WC, Semb G. Eurocleft - An experiment in intercenter collaboration. In: Berkowitz, S: Cleft lip and palate. Berlin Heidelberg: Springer; 2006:765-776.

Chapter 8

Summary

Summary

Chapter 1 introduces the topic of cleft lip and palate to the reader. Types of clefts, incidence and etiology are briefly discussed. Moreover, general aspects of the UCLP (UCLP = Unilateral Cleft Lip and Palate) malformation like its maxillofacial characteristics are described. The multidisciplinary treatment of patients with a UCLP in a cleft team as well as the effect of palatal surgery on further maxillofacial growth and development are discussed. The background of this thesis is elucidated by a description of the evaluation of treatment outcome in UCLP performed over the past years. An overview of the present thesis is presented.

Chapter 2 evaluates the dental arch relationships of a group of 43 patients with a complete UCLP from the Cleft Palate Craniofacial Unit of Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. The dental arch relationships were evaluated at the age of 9 years with the help of the GOSLON Yardstick. All Nijmegen patients were treated with a 2-stage palatal closure: soft palate closure at 11 to 13 months of age, hard palate closure at 4 to 11 years of age. The Nijmegen GOSLON scores were compared with the GOSLON outcomes of the six individual centers (A-F) from the Eurocleft study, and possible relationships between treatment protocols and GOSLON outcomes were evaluated. For the Nijmegen UCLP group, it was found that 9% of dental arch relationships had a GOSLON score of 1, 52% had a score of 2, 30% has a score of 3, 9% had a score of 4, and none had a score of 5. The mean Nijmegen GOSLON score (2.36, SD 0.74) showed no significant differences with Eurocleft centers A, B and E, which achieved the best treatment results, but did significantly differ from GOSLON outcomes of Eurocleft centers D ($p<0.001$), C and F ($p<0.01$), which had relatively poor treatment outcome. Nijmegen and the best Eurocleft centers A, B and E had high volume operators but treatment protocols were not the same. The protocols of Nijmegen and center A with delayed hard palate closure differed substantially from the protocols of Eurocleft centers B and E where the anterior hard palate was closed at the age of 2 to 3 months. Treatment outcome of the Nijmegen patients with UCLP and treated with two-staged palatal closure including delayed closure of the hard palate was comparable to the results of the Eurocleft centers with the best outcome. Treatment protocol could not explain differences in the quality of treatment results.

The aim of the investigation described in **Chapter 3** was to assess determinants for treatment outcome in UCLP, rated according to the GOSLON Yardstick and “GOSLON-like” 5-year-index by means of a meta-analysis. Multiple databases were searched for publications in which patient groups were evaluated by GOSLON ranking or the “GOSLON-like” 5-year index. Based on the inclusion criteria, 15 publications were selected, and the following background variables could be extracted that were evaluated as determinants for treatment outcome in UCLP: year of birth, average age of the patient group, racial background, presence of Simonart’s band, use of infant orthopedics, palate closure before the age of 3 years versus palatal closure at a later age, alveolar bone grafting and number of surgeons. The total number of patients included in the meta-analysis was 1236. The only background variable with a significant (p=0.003) influence on the treatment outcome was the timing of palatal closure. Patients whose soft and hard palate were closed before the age of 3 years presented poorer GOSLON scores (mean score 2.9, SD 0.4) than patients whose hard palate closure was performed at a later age (mean GOSLON score 2.3, SD 0.2). Of all patients in the early palatal closure group, 29% were allocated a GOSLON score 4 or 5 versus only 4% of the patients treated with a delayed palatal closure procedure. So, when compared with delayed hard palate closure, 25% more patients required complex orthodontics or an ortho-surgical approach in case of early palatal closure. Well-designed, randomized clinical trials (RCTs) are required, however, for further investigation of the optimal timing for palatal closure.

Chapter 4 investigates the reliability of using photographs of study casts as an alternative to casts for rating dental arch relationships in UCLP. Records of 49 consecutive patients with a complete UCLP at the age of 9 years were used from the Cleft Palate Craniofacial Unit of the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. The dental casts as well as their corresponding photographs were scored independently by four observers, using the GOSLON

Yardstick as rating system. A high intra- and inter-observer agreement was found for the GOSLON classification on dental casts as well as on their corresponding photographs. No significant differences were found between the GOSLON ratings of dental casts when compared with GOSLON ratings applied to the photographs of these dental cast. Thus, photographs of dental casts provide a consistent, reproducible method for rating dental arch relationships in patients with UCLP, and provide a reliable alternative to the application of the GOSLON Yardstick on dental casts. Testing of this new method showed that dental arch relationships in UCLP could be reliably rated on the Internet using photographs of dental casts, which will facilitate future evaluation and comparison of treatment outcome in cleft care.

Chapter 5 evaluates the nasolabial appearance of the Nijmegen patients with a complete UCLP, and compares this esthetic outcome with the esthetic results of the six individual centers from the Eurocleft study. This was done with the aim to select patients with the best treatment outcome for the international good practice archive, which is part of the EUROCRAN project. For the Nijmegen patients, relationships between ratings in nasolabial esthetics and dental arch relationships were also investigated. The nasolabial appearance of 42 consecutive Nijmegen patients with a complete UCLP was assessed by applying the Asher-McDade esthetic index at the age of 9 years. This index has also been used in the Eurocleft study, and consists of 4 different components (nasal deviation, nose form, vermilion border, nasal profile), which are scored separately on a 5-point-scale and subsequently averaged to an overall esthetic score (also on a 5-point scale with 1=very good nasolabial appearance to 5=very poor nasolabial appearance). The mean of the overall esthetic rating of the Nijmegen patients was 3.0 with a 90% central range from 2.0 to 3.7 on a scale from 1 to 5. With regard to the overall esthetic rating, Nijmegen showed similar treatment outcomes with Eurocleft centers A, D, E and F; Nijmegen scored significantly better than Eurocleft center C and significantly worse than Eurocleft center B ($p \leq 0.05$). Comparisons of treatment protocol could not explain differences in nasolabial appearance between Nijmegen and the Eurocleft centers. Within the Nijmegen patient group, no significant correlations between esthetic ratings and dental arch relationships could be established. The current comparative study is supportive in the selection of patient records that are suitable for the “good practice archive”, which is part of the EUROCRAN project.

Chapter 6 describes a long-term cephalometric study aimed to evaluate the craniofacial development of the Nijmegen patients with a complete UCLP and treated with 2-stage palate closure, including delayed closure of the hard palate. Prediction models for cephalometric outcome at age 18 were developed with cephalometric values at the ages 9 and 12 years. Moreover, the objective need for surgery at age 18 was predicted from cephalometric values at age 9 with the help of logistic regression analysis. Cephalograms of 43 consecutive patients with a complete UCLP from the Nijmegen Cleft Unit were analyzed at 9, 12 and 18 years. The patient group showed a retrusive craniofacial growth pattern for the maxilla and mandible, and a rather vertical growth pattern for the lower face. Using multiple linear regression, for most cephalometric variables, 40 to 80% of the cephalometric values at early adulthood could be explained by cephalometric values at the ages 9, 12, and gender or by the cephalometric values at age 9 only, and gender. Several cephalometric variables at age 9 (s-n-ss, s-n-pg, sss-ns-sms, sss-ns-pgs) were found significant predictors for the need for surgery at age 18. Moreover, the need for surgery at age 18 was correctly predicted from age 9 for 85% of the investigated patient group with the help of logistic regression analysis. Application of the current logistic regression analysis on another comparative cleft group would assess the true power of the prediction model.

In **Chapter 7**, a general discussion is given on the problems encountered during this study as well as on the results found in the different parts of the thesis. The concept of 2-staged palate repair including delayed closure of the hard palate, which has been applied to the investigated Nijmegen patient group, is extensively discussed and related to literature. Concerns regarding speech and additional burdens of care might justify a 2-staged palate repair with an earlier closure of the hard palate than the age of 9 years, which is the current age at which hard palate closure is performed for the Nijmegen cleft group. However, prospective, well-designed controlled studies, especially on long-term results, are urgently needed to take an evidence-based decision on timing of hard palate repair.

Chapter 9

Samenvatting

Samenvatting

Hoofdstuk 1 is een introductie op het onderwerp schisis. De verschillende typen schisis, de incidentie en de etiologie worden kort beschreven. Daarnaast worden algemene aspecten van de enkelzijdige schisis (UCLP = Unilateral Cleft Lip and Palate) beschreven zoals de maxillofaciale kenmerken, de multidisciplinaire behandeling door een schisisteam alsook het effect van gehemeltechirurgie op de verdere maxillofaciale groei en ontwikkeling. De achtergrond van dit proefschrift wordt toegelicht vanuit de evaluatie van behandelingsresultaten in UCLP over de afgelopen jaren. Een overzicht van het huidige proefschrift wordt gepresenteerd.

In **Hoofdstuk 2** wordt een onderzoek beschreven naar de kaakrelatie van een groep van 43 patiënten met een complete UCLP die behandeld zijn in het Centrum voor Schisis en Aangeboren Schedel- en Gelaatsafwijkingen van het UMC St Radboud in Nijmegen. De kaakrelatie werd op 9-jarige leeftijd geëvalueerd met behulp van de GOSLON Yardstick. Alle patiënten werden behandeld met een 2-fase gehemeltesluiting waarbij het zachte gehemelte op de leeftijd van 11 tot 13 maanden gesloten werd en het harde gehemelte op de leeftijd van 4 tot 11 jaar. De Nijmeegse GOSLON scores werden vergeleken met de GOSLON scores van de zes centra (A t/m F) van de Eurocleft studie en mogelijke relaties tussen de verschillende behandelingsprotocollen en GOSLON scores werden geëvalueerd. Van de Nijmeegse patiëntengroep had 9% een GOSLON score 1, 52% een score 2, 30% een score 3, 9% een score 4 en geen van de patiënten had een GOSLON score 5. De gemiddelde Nijmeegse GOSLON score (2,36; SD 0,74) verschilde niet van Eurocleft centra A, B en E die in de Eurocleft studie het beste scoorden. De Nijmeegse GOSLON scores vertoonden een significant verschil met de Eurocleft centra D ($p<0.001$), C en F ($p<0.01$) die slecht scoorden in de Eurocleft studie. In Nijmegen en de beste Eurocleft centra werken chirurgen die een groot aantal kinderen per jaar behandelen, maar de gehanteerde behandelingsprotocollen waren niet gelijk. Nijmegen en Eurocleft centrum A hanteerden een late harde gehemeltesluiting terwijl bij Eurocleft centrum B en E het harde gehemelte op de leeftijd van 2 tot

3 maanden werd gesloten. Geconcludeerd werd dat het behandelingsresultaat van de Nijmeegse patiënten met een 2-fase gehemeltesluiting inclusief late sluiting van het harde gehemelte vergelijkbaar was met de resultaten van de Eurocleft centra met het beste behandelresultaat. De gehanteerde behandelingsprotocollen konden de verschillen in behandelingsresultaat echter niet verklaren.

Het doel van het in **Hoofdstuk 3** beschreven onderzoek was om met behulp van een meta-analyse te bepalen welke factoren doorslaggevend zijn voor het behandelingsresultaat van patiënten met een UCLP. Als maat voor het behandelingsresultaat werden de GOSLON Yardstick en de 5-Year-Index gebruikt. Diverse elektronische databases werden doorzocht op publicaties waarin één of meerdere groepen patiënten met UCLP werden geëvalueerd met behulp van de GOSLON Yardstick en/of de 5-Year-Index. Vijftien publicaties voldeden aan de inclusiecriteria. Per patiëntengroep werden de volgende variabelen geëvalueerd als mogelijke factoren voor het behandelingsresultaat: het gemiddelde geboortejaar van de geëvalueerde patiëntengroep (voor/na 1985), ras (alle patiënten Kaukasisch ja/nee), patiënten met een Simonart's bandje (ja/nee), prechirurgische orthopedie (ja/nee), tijdstip van gehemeltesluiting (vóór driejarige leeftijd/na driejarige leeftijd), bottransplantaat (bij geen patiënten/bij een aantal patiënten/bij alle patiënten) en het aantal betrokken chirurgen (t/m 3 chirurgen/>3 chirurgen). Het totale aantal geëvalueerde patiënten in deze meta-analyse was 1236. Alleen voor de variabele "tijdstip van gehemeltesluiting" werd een significante (p=0,003) invloed op het behandelingsresultaat gevonden. Patiënten waarbij het zachte en harde gehemelte gesloten werden vóór de leeftijd van 3 jaar vertoonden significant minder goede GOSLON scores (gemiddelde GOSLON score 2,9; SD 0,4) dan patiënten waarbij het harde gehemelte na driejarige leeftijd werd gesloten (gemiddelde GOSLON score 2,3; SD 0,2). Van alle patiënten met een vroege gehemeltesluiting werd aan 29% een GOSLON score 4 of 5 toegekend versus slechts 4% van de patiënten met een late harde gehemeltesluiting. In geval van vroege gehemeltesluiting hebben dus 25% méér patiënten een complexe orthodontische of een gecombineerde orthodontisch-chirurgische aanpak nodig in vergelijking met late harde gehemeltesluiting. Goed opgezette randomized clinical trials zijn vereist om in toekomstig onderzoek het beste tijdstip van gehemeltesluiting te bepalen.

In **hoofdstuk 4** wordt de betrouwbaarheid van het gebruik van foto's van gebitsmodellen als alternatief voor fysieke gebitsmodellen voor het classificeren van kaakrelaties van patiënten met unilaterale schisis onderzocht. Hiervoor werden gebitsmodellen op de leeftijd van 9 jaar gebruikt van 49 opeenvolgende patiënten met een UCLP uit het Centrum voor Schisis en Aangeboren Schedel- en Gelaatsafwijkingen van het UMC St Radboud te Nijmegen. Zowel de gebitsmodellen als de foto's van dezelfde gebitsmodellen werden onafhankelijk van elkaar gescoord door 4 beoordelaars waarbij gebruik gemaakt werd van de GOSLON Yardstick als classificatiesysteem. Er werd zowel voor de GOSLON scoring op de gebitsmodellen alsook voor de GOSLON scoring op de foto's van de gebitsmodellen een hoge "intra- en interobserver" overeenstemming gevonden. Verder werden er geen significante verschillen gevonden tussen de GOSLON scoring op gebitsmodellen en de GOSLON scoring op foto's van dezelfde gebitsmodellen. Foto's van gebitsmodellen bleken een consistent en reproduceerbaar medium om kaakrelaties van patiënten met een UCLP te classificeren en vormen een betrouwbaar alternatief voor de toepassing van de GOSLON Yardstick op gebitsmodellen. Toetsing van deze nieuwe methode liet zien dat unilaterale kaakrelaties via Internet betrouwbaar geclassificeerd kunnen worden met behulp van foto's van gebitsmodellen, hetgeen evaluatie en vergelijking van behandelingsresultaten op het gebied van schisis in de toekomst kan vergemakkelijken.

In **hoofdstuk 5** wordt de nasolabiale esthetiek van de Nijmeegse patiënten met een complete UCLP geëvalueerd en vergeleken met de esthetische resultaten van de zes individuele centra van de Eurocleft studie. Dit werd gedaan met de doelstelling patiënten met het beste behandelingsresultaat te selecteren voor het internationale "good practice archive", wat onderdeel uitmaakt van het EUROCAN project. Daarnaast werd voor de Nijmeegse patiënten ook de samenhang tussen nasolabiale esthetiek en kaakrelatie onderzocht. De nasolabiale esthetiek van 42 opeenvolgende patiënten met een complete UCLP werden op 9-jarige leeftijd geëvalueerd met behulp van de Asher-McDade esthetische index.

Deze esthetische index werd ook in de Eurocleft studie gebruikt en bestaat uit 4 afzonderlijke componenten (symmetrie van de neus, vorm van de neus, lippenrood en het nasolabiale profiel) die afzonderlijk gescoord worden op een 5-puntsschaal en vervolgens gemiddeld tot een totale esthetische score (ook een 5-puntsschaal waarbij 1=zeer goede nasolabiale esthetiek, 5=erg slechte nasolabiale esthetiek). Het gemiddelde van de totale esthetische scores voor de Nijmeegse patiënten is 3,0 met een 90% concentratie-interval tussen 2,0 en 3,7. Met betrekking tot de totale esthetische scoring vertoonde Nijmegen een esthetisch behandelingsresultaat vergelijkbaar met de Eurocleft centra A, D, E en F; Nijmegen scoorde significant beter dan Eurocleft centrum C en significant slechter dan Eurocleft centrum B ($p \leq 0.05$). Vergelijking van de behandelingsprotocollen kon de verschillen in nasolabiale esthetiek tussen Nijmegen en de Eurocleft centra niet verklaren. Voor de Nijmeegse patiënten konden geen significante correlaties worden vastgesteld tussen de nasolabiale esthetiek en de kaakrelaties. De huidige, vergelijkende studie dient ter ondersteuning voor het selecteren van geschikt patiëntenmateriaal voor het "good practice archive" dat onderdeel uitmaakt van het EUROCRAN project.

In **Hoofdstuk 6** wordt een longitudinale cephalometrische lange-termijn studie beschreven waarin de craniofaciale ontwikkeling wordt geëvalueerd van de Nijmeegse patiënten met UCLP die met een 2-fase gehemeltesluiting inclusief een late sluiting van het harde gehemelte behandeld werden. Modellen werden ontwikkeld om de cephalometrische waarden op de leeftijd van 18 jaar te voorspellen met behulp van de cephalometrische waarden op de leeftijd van 9 en 12 jaar. Daarnaast werd met behulp van logistische regressietechnieken op basis van de cephalometrische waarden op 9-jarige leeftijd de objectieve noodzaak voor chirurgie op 18-jarige leeftijd voorspeld. Cephalogrammen van 43 opeenvolgende patiënten met een complete UCLP uit het Centrum voor Aangeboren Schedel- en Gelaatsafwijkingen van het UMC St Radboud te Nijmegen werden geanalyseerd op 9, 12 en 18-jarige leeftijd. De Nijmeegse groep met enkelzijdige schisis liet een terugliggend craniofaciaal groeipatroon voor de boven- en onderkaak zien met een verticaal groeipatroon voor de onderste gezichtshelft. Met behulp van multiple lineaire regressie kon voor de meeste cephalometrische variabelen, 40 tot 80% van de cephalometrische waarden op 18-jarige leeftijd worden voorspeld uit de cephalometrische waarden op 9 en 12-jarige leeftijd in combinatie met geslacht of uit de cephalometrische waarden op alleen 9 jaar in combinatie met geslacht. Verscheidene cephalometrische waarden op 9-jarige leeftijd (s-n-ss, s-n-pg, sss-ns-sms, sss-ns-pgs) waren significante voorspellers voor de noodzaak voor chirurgie op 18-jarige leeftijd. Daarnaast werd met behulp van logistische regressie analyse de noodzaak voor chirurgie op 18-jarige leeftijd voor 85% van de onderzochte patiëntengroep correct voorspeld op basis van cephalometrische waarden op 9-jarige leeftijd. Toepassing van de huidige, logistische regressie-analyse op een andere, vergelijkbare schisisgroep bepaalt de ware kracht van het voorspellingsmodel.

In **Hoofdstuk 7** wordt een algemene discussie gegeven over zowel de problemen ondervonden tijdens deze studie alsook over de resultaten die in de verschillende delen van dit proefschrift gevonden zijn. Het concept van 2-fase gehemeltesluiting inclusief late sluiting van het harde gehemelte, dat is toegepast op de onderzochte Nijmeegse patiëntengroep wordt uitvoerig bediscussieerd en gerelateerd aan de literatuur. De spraakkwaliteit en de extra zorglast zouden eerdere sluiting van het harde gehemelte dan de huidige leeftijd van 9 jaar voor de Nijmeegse patiëntengroep kunnen rechtvaardigen. Prospectieve, goedopgezette studies, vooral over de lange termijn resultaten, zijn echter dringend nodig om een evidence-based beslissing te nemen over het tijdstip van harde gehemeltesluiting.

Dankwoord

Prof. dr. A.M. Kuijpers-Jagtman. Beste Anne Marie, met betrekking tot de begeleiding van dit onderzoek ben ik jou de meeste dank verschuldigd. Graag wil ik je vanaf deze plaats hartelijk bedanken voor je efficiënte en vriendelijke begeleiding.
Prof. dr. C. Katsaros. Beste Christos, jij hebt mijn promotie van het begin tot het einde meegemaakt. Ik wil je hartelijk bedanken voor je participatie en supervisie gedurende het hele traject.
Prof. dr. M. van ’t Hof en dr. ir. E.M. Bronkhorst. Beste Martin, bedankt voor je vele toverwerk met getallen en dat je altijd voor me klaar stond. Beste Ewald, jammer dat onze samenwerking is afgelopen want naast statistiek zijn we ook over onze gemeenschappelijke hobby, de blaasmuziek, nog lang niet uitgepraat.
Prof. dr. W.C. Shaw en prof. dr. G. Semb. Dear Bill and Gunvor, thank you so much for the nice collaboration and... my linguistic skills have been improved!
Beste Annet, Sjoerd, Rinske, Solla en Mattijs. Met veel plezier kijk ik terug op al onze gemeenschappelijke activiteiten, zowel binnen als buiten de werksfeer, die we tijdens onze opleidingstijd tot orthodontist hebben ondernomen. Ik heb jullie collegiale houding in onze geweldige groep altijd bijzonder gewaardeerd!
Langs deze weg wil ik alle medewerkers van de afdeling Orthodontie en Orale Biologie bedanken voor de hulp en gezelligheid van de afgelopen jaren. “Onze” klinische supervisoren Johanna Maertens, René Noverraz, Annemarie Renkema en Maarten Wijdeveld wil ik bedanken voor hun deskundige klinische begeleiding. De opleidingsgroepen voor en na ons, “onze senioren” Rima, Katja, Diego, Isolde en Patricia en “onze junioren” Marieke, Aniek, Ron, Richard, Robbert, Christos, Elke en Afien voor de plezierige contacten. Athina Chatzigianni en Stephanie Delbauve voor de fijne samenwerking tijdens dit onderzoek. Yvonne Kievits voor de uitstekende hulp bij de opmaak van dit boekje.
Mijn vrienden Dennis, Erik, Jan-Willem, Joost en Stefan dank ik voor hun gezelligheid tijdens het bijna-dagelijkse samen eten, gemeenschappelijke vakanties, etc. Shoghi voor het “buurten”, vaak op

zaterdagavond met de nodige humor; Karlijn voor de hartelijke vriendschap “op afstand”.
Alle vrienden en kennissen via *Qharmony* en *Muziekvereniging TNT Nijmegen* voor het samen delen van lief en leed tijdens en na het uitoefenen van een gemeenschappelijke hobby.
Mijn ouders dank ik voor al hun hulp en interesse die ik mijn hele leven altijd heb mogen ontvangen en voor de prettige contacten die er nog steeds zijn. Bij dit laatste wil ik ook Pettie, Liselotte en Dennis betrekken.
Franca, jij was al gepromoveerd voordat ik met mijn specialisten-opleiding in Nijmegen begon. Jouw nimmer aflatende begrip, steun en interesse zijn niet in een paar woorden te vangen en strekken zich ver over de horizon van het doen van onderzoek uit. Bedankt voor alles!

Over de auteur...

Pieter Nollet werd op 11 februari 1975 geboren te Utrecht. Na het eindexamen VWO in 1993 aan het Eykhagencollege te Landgraaf, ging hij tandheelkunde studeren aan de Radboud Universiteit Nijmegen waar hij in 1997 zijn doctoraalexamen en in 1998 zijn tandartsexamen behaalde. Tijdens zijn studententijd was hij een van de oprichters van *Qharmony*, het universitair harmonieorkest, waar hij een aantal jaren in het bestuur zat.

Vanaf september 1998 tot en met juli 2001 werkte hij full-time als tandarts, in de algemene praktijk en in justitiële inrichting *De Hunnerberg* te Nijmegen. Naast zijn werkzaamheden als tandarts volgde hij diverse cursussen waaronder de 2-jarige weekendcursus *Progressive Orthodontic Seminars (POS)* in Amstelveen.

Van 2001 tot 2005 volgde hij de vierjarige full-time specialistenopleiding tot orthodontist. Momenteel is hij als orthodontist werkzaam in diverse orthodontiepraktijken alsook op de afdeling orthodontie van het *Sophia Kinderziekenhuis* te Rotterdam. Hij presenteerde onderzoek uit dit proefschrift verschillende keren voor de Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA), tijdens het European Congress on Craniofacial Anomalies in Bologna, Italië (2003), en tijdens de EOS-congressen in Aarhus, Denemarken (2004), Amsterdam, Nederland (2005) en Wenen, Oostenrijk (2006).

About the author...

Pieter Nollet was born in Utrecht, the Netherlands on the 11th of February 1975. In 1993 he finished his pre-university education at the Eykhagencollege in Landgraaf, the Netherlands. Subsequently, he studied dentistry at the Radboud University Nijmegen where he obtained his Master's degree in 1997 and his dentist's degree in 1998. During his studies, he co-founded *QHarmony*, the university harmony orchestra, where he was a member of the Board for three years.

From September 1998 to July 2001, he worked as a dentist in general practice and, for half a day per week, in the penitentiary *De Hunnerberg* in Nijmegen. Moreover, he followed various courses in different fields of the profession among which the *Progressive Orthodontic Seminars (POS)* over a period of two years.

From 2001 to 2005 he followed the 4-year full-time postgraduate training in orthodontics. He currently works as an orthodontist in orthodontic practices as well as at the orthodontic department of the *Sophia Kinderziekenhuis* in Rotterdam. He presented research from this thesis several times at the annual meetings of the Dutch Cleft Palate Association, the European Congress on Craniofacial Anomalies in Bologna, Italy (2003), and the EOS-Congresses in Aarhus, Denmark (2004), Amsterdam, the Netherlands (2005), and Vienna, Austria (2006).